THE LIVER IN ULCERATIVE COLITIS
THE SIGNIFICANCE OF RAISED SERUM-ALKALINE-PHOSPHATASE LEVELS

R. W. BODEN
M.B. Sydney, M.R.A.C.P.
FELLOW

J. G. RANKIN
M.B. Sydney
REGISTRAR

S. J. M. GOULSTON
M.C., M.B. Sydney, M.R.C.P., F.R.A.C.P.
HONORARY ASSISTANT PHYSICIAN

Sir WILLIAM MORROW
D.S.O., M.B. Sydney, F.R.C.P., F.R.A.C.P.
HONORARY PHYSICIAN

From the Gastro-Enterology Clinic, Royal Prince Alfred Hospital, Sydney*

FUNCTIONAL and organic changes in the liver of patients with non-specific ulcerative colitis have often been reported. Pollard and Block (1948) recall that even before the first description of ulcerative colitis as a clinical entity by Wilks and Moxom (1875), Thomas (1874) described a case of ulceration of the colon associated with fatty infiltration of the liver, and that Lister in 1899 recorded a case of diffuse ulcerative colitis complicated by acute interstitial hepatitis. It is generally agreed that fatty infiltration of the liver is common in ulcerative colitis but there is less agreement about the nature and prevalence of other hepatic complications. A pathological picture consistent with pericholangitis or interlobular hepatitis, though mentioned by others, has been emphasised only by Kleckner et al. (1952) and Kimmelstiel et al. (1952).

Among patients with liver disease who had serum-alkaline-phosphatase levels above 50 King Armstrong (K.A.) units per 100 ml. we noted that some were suffering from non-specific ulcerative colitis. Reviewing 190 cases of ulcerative colitis seen in the Gastro-Enterology Clinic of the Royal Prince Alfred Hospital in 1950–58, we found 11 such cases. This report is concerned with the ætiology and pathology of the liver disease in these patients, and with its clinical implications.

Methods

The patients were admitted to this hospital on one or more occasions; and the diagnosis of ulcerative colitis was confirmed in each of them by barium-enema examination, sigmoidoscopy, and rectal biopsy. The colon was examined after colectomy in 3 cases and at necropsy in 2.

Clinical evidence of liver disease was found in 9 cases. In 7 it had been the reason for their admission. Of the 4 cases (nos. 3, 7, 9, 10) admitted for treatment of their colitis, 2 (nos. 7 and 10) developed clinical liver disease while in hospital.

Liver dysfunction was confirmed biochemically by estimations of serum-proteins, serum-bilirubin, serum-alkaline-phosphatase, thymol flocculation, zinc-sulphate turbidity, and bromsulphalein retention. The total serum-cholesterol was also estimated. The results are shown in table I. Sections for microscopy were obtained in all cases except case 3—by percutaneous biopsy, at laparotomy, or at necropsy.

Laparotomy was performed in 9 cases, and the biliary tree was specifically examined in 5. Of the other 6, 2 had patent ducts at necropsy; but in 4 (nos. 3, 4, 6, 10) obstruction to the biliary tree could not be ruled out.

* Supported by a grant from an anonymous donor.

Findings

In this series we found several types of liver disease. We shall exclude the following 4 cases from discussion because of lack of conclusive evidence of pericholangitis, or because they had some complicating disease.

In case 3 the elevated serum-alkaline-phosphatase was a chance finding. At laparotomy the liver was macroscopically normal, and no biopsy specimen was taken. The high phosphatase therefore remains unexplained, but the patient's liver-function tests remain abnormal; and we feel that she is a case of pericholangitis. She has been excluded from that group because she has had no liver biopsy.

In case 9 the postmortem finding of a secondary mucus-secreting adenocarcinoma from an unknown primary site, without evidence of hepatic involvement, again leaves the cause of the raised serum-phosphatase unexplained.

In case 10 colitis was severe at the time of the rise in serum-alkaline-phosphatase, but in this patient an additional diagnosis of infectious mononucleosis was made on clinical grounds and on finding unclassifiable cells in the blood.

Case 6 was seen in the terminal stages of liver disease with a five-year history of jaundice. We do not know whether the bile-ducts were explored at the time of cholecystectomy.

In the remaining 7 patients (cases 1, 2, 4, 5, 7, 8, 11) the diagnosis of pericholangitis was made on the initial hepatic biopsy. In all 7 the colonic disease was mild or moderately severe, the only complications being anæmia due to chronic blood-loss in cases 7 and 8, and arthritis with an erythematous rash in case 4.

No patient received a blood-transfusion before the onset of liver disease and the possibility of serum hepatitis has been excluded.

The colitis involved the whole colon in 5 patients and only the left half in 2. No patient had rectosigmoiditis or enterocolitis.

A two-stage proctocolectomy was performed in case 7: the patient was jaundiced before colectomy and had a serum-alkaline-phosphatase of 62 K.A. units. Liver-function tests were next performed after resection of the rectum, when the alkaline-phosphatase level had fallen to 23 K.A. units; but at this stage the clinical picture was complicated by hæmolysis with anuria. At necropsy this patient had biliary cirrhosis without obstruction to the biliary tree. No other patient in this group had surgery for colitis. It was not possible to correlate exacerbations of diarrhœa with jaundice.

Clinical evidence of liver disease was first noticed six months to seventeen years after the onset of colitis. Only in case 1 was liver disease evident before the onset of colitis; and this patient, when first seen, had a significant elevation of his brucella agglutination titre. Liver disease and colitis have continued since that time with a persistently negative titre.

Symptomatically liver disease was episodic in all cases, the duration to the present time or necropsy varying from three to twenty-six years. 6 cases had one or more attacks of jaundice, which were usually long. A clinical episode resembling cholangitis occurred in 3 (cases 1, 2, 8), no extrahepatic biliary obstruction being found at operation. All patients had persistent hepatomegaly and 4 had splenomegaly. Splenomegaly was associated with portal hypertension in cases 5 and 11. Ascites supervened in case 5, a patient with advanced cirrhosis. Other complications of liver disease were hæmorrhage from œsophageal varices in cases 5 and 11, hepatic coma in cases 5 and 8, and uræmia in cases 7 and 8.

TABLE I—CLINICAL AND LABORATORY INVESTIGATIONS* IN PATIENTS WITH ULCERATIVE COLITIS AND HEPATITIS

No.	Age	Sex	Duration of colitis (yr.)	Duration of liver disease (yr.)	Severity and extent of colitis	Hepatomegaly	Splenomegaly	Jaundice	Serum-proteins (g. per 100 ml.)	Bilirubin (mg. per 100 ml.)	Serum-alkaline-phosphatase (K.A. units)	Thymol flocculation	Zinc-sulphate turbidity	Serum-cholesterol (mg. per 100 ml.)	Bromsulphalein retention (%)	Pathological diagnosis
1	48	M	26	26	Mild; left-sided	+	+	+	6·5 9·0	0·2 4·5	15 93	− 3+	9 20	130 290	.. ..	Pericholangitis
2	29	M	20	3	Moderate; whole colon	+	+	+	6·0 7·9	0·4 16·6	83 160	+ 4+	4 10	190 390	.. ..	Pericholangitis
3	37	F	20	..	Mild; whole colon	−	−	−	8·6 ..	0·6 1·4	32 62	.. 3+	8 14	.. 260	.. ..	No liver biopsy
4	35	M	10	3/12	Mild; left-sided	+	−	+	.. 8·6	0·6 8·0	58 63	2+ 4+	.. 25	.. 410	.. ..	Pericholangitis
5	53	F	13	7	Mild; whole colon	+	+	+	4·0 7·7	4·6 27·7	15 64	+ 4+	6 38	130 640	.. ..	Pericholangitis later developing cirrhosis
6	53	M	20	5	Moderate; whole colon	+	+	+	7·4 8·0	4·5 6·5	46 50	.. 3+	12 17	.. ..	24 ..	Cirrhosis
7	24	M	9	8	Moderate; whole colon	+	−	+	7·1 7·8	1·0 4·4	23 62	.. 2+	3 12	.. ..	.. 60	Pericholangitis later developing biliary cirrhosis
8	55	M	11	10	Moderate; whole colon	+	−	+	5·5 7·9	0·2 46·0	24 102	.. ..	2 7	.. ..	.. ..	Pericholangitis and cholangiocarcinoma
9	24	M	2	..	Moderate; whole colon	−	−	−	6·7 7·0	.. 0·2	.. 60	.. ..	.. ..	.. ..	.. ..	Secondary carcinoma
10	26	F	11	1/2	Moderate; whole colon	+	+	−	5·1 6·0	0·2 ..	7 57	.. 2+	3 6	150 ..	12 20	Infectious mononucleosis
11	27	M	15	1/2	Mild; whole colon	+	+	−	5·9 7·5	0·4 0·7	41 58	+ 3+	5 8	.. 355	.. 18	Pericholangitis

* Maximum and minimum values.

The colitis was not sufficiently severe to cause hypoproteinæmia while the patients were under observation; but the plasma-proteins did fall during the terminal liver disease in cases 5 and 8.

In cases 2 and 4 the serum-alkaline-phosphatase level was always higher than 50 K.A. units: in the remaining 5 patients it varied considerably but rose to above 50 at some stage of their illness. Correlation with the serum-bilirubin levels was not close.

Thymol flocculation was initially normal in cases 1, 5, 7, and 8, with progressive elevation to abnormal levels in cases 1 and 5. Cases 2, 4, and 11 had abnormal flocculation on first admission; but in cases 2 and 11 it returned to normal.

Zinc-sulphate turbidity has always been normal in cases 2, 8, and 11 since the patients were first seen. It was high initially in cases 1, 5, and 7, although in cases 1 and 5 there was a long period of illness before the test was performed, and during this early period the thymol-flocculation test had remained normal. Persistently high levels were found in case 1; whereas there was gradual fall to normal levels with terminal liver disease in cases 5 and 7. In cases 3 and 4 zinc-sulphate turbidity was first performed recently: it was elevated in both.

Serum-cholesterol was estimated in 6 cases and was at or above the upper limit of normal in all.

The prothrombin index was normal in all cases; nor did routine hæmatological investigation reveal any significant abnormality.

In 3 cases which came to necropsy with progressive liver disease obstruction to major ducts of the biliary system was excluded.

In case 7 biliary cirrhosis was found.

In case 5 the findings were advanced cirrhosis with hyperplasia of the bile-ducts and with bile stasis. This patient had had an operative liver biopsy some two years earlier: it had shown cholangitis, fatty change, and early cirrhosis.

In case 8 death was from hepatorenal failure. At necropsy portal fibrosis, small areas of hepatic necrosis, and a metastasising cholangiocarcinoma were found.

Discussion

In a series of 190 cases of non-specific ulcerative colitis, seen at the Royal Prince Alfred Hospital, 33 had evidence of hepatic disease on biopsy or at necropsy. The lesions are shown in table II. Of those with serum-alkaline-phosphatase levels over 50 K.A. units 7 had pericholangitis : 2 of these developed cirrhosis and 1 a cholangiocarcinoma. We feel that the diagnosis of pericholangitis can be made in such patients if the biochemical, histological, and clinical picture is recognised.

Clinically the patients may show no sign of liver disease, or they may present with a history of one or more long attacks of jaundice, sometimes associated with pruritus and episodes of fever and pain in the right hypochondrium suggestive of cholangitis. In the presence of jaundice the liver is enlarged, with or without splenomegaly. The jaundice is intermittent; but even during remission there may still be pruritus, hepatomegaly, and splenomegaly.

The outstanding feature of the liver-function tests is their "obstruetive profile": in our cases the serum-alkaline-phosphatase reached maximum values between

TABLE II—LIVER DISEASE IN 190 CASES OF ULCERATIVE COLITIS

Type		Numbers
Hepatitis	Infective	3
	Serum	1
	Infectious mononucleosis	1
	Focal (at necropsy)	3
Pericholangitis		11
Cirrhosis	Undetermined ætiology	4
	Following pericholangitis	2
	Postinfective	1
Cholangiocarcinoma		1
Fatty infiltration		9

Patients who have had only their non-specific protein reactions raised have been excluded. 2 have had raised serum-alkaline-phosphatase levels to 24 K.A. units without other abnormality.

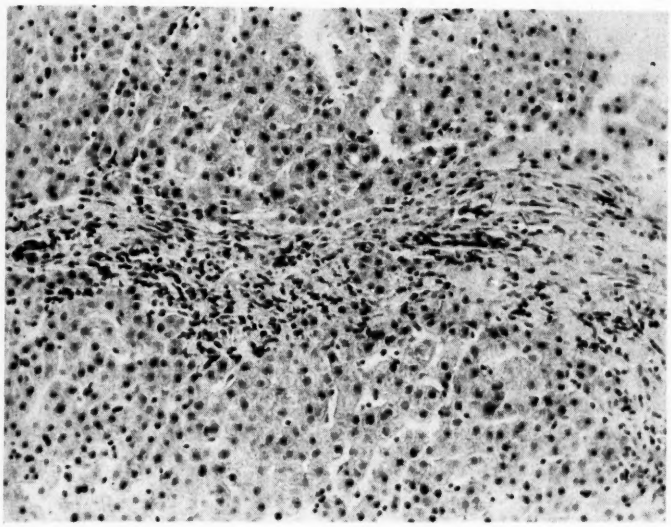

Fig. 1—Photomicrograph showing an increase in the fibrous tissue in the portal tract with inflammatory infiltration.

50 and 160 K.A. units. Pericholangitis can, however, occur without such a rise.

The typical histological picture is a portal and periportal inflammation, sometimes associated with hepatocellular degeneration with or without fibrosis (figs. 1 and 2). This lesion may resolve completely, leave slight residual fibrosis, or gradually progress to biliary cirrhosis.

Most investigators have found a high incidence of liver disease—especially of cirrhosis and fatty infiltration—in patients with ulcerative colitis. This has usually been attributed to severe colitis associated with anæmia, hypoproteinæmia, toxæmia, and malnutrition. Often, however, liver disease complicates mild ulcerative colitis (Kimmelstiel et al. 1952, Kleckner et al. 1952); and even severe forms cannot explain all types of liver involvement. In particular, they cannot account for pericholangitis.

Kleckner et al. (1952) in 32 liver biopsies from patients suffering from ulcerative colitis found pericholangitis in 8 cases—in 3 uncomplicated, in 3 with bile stasis, and in 2 with diffuse hepatitis and periportal inflammation. The first 3 had no clinical or biochemical evidence of liver disease, whereas long-continued jaundice was a feature in the remaining 5. These authors felt that infectious hepatitis and homologous-serum jaundice had been adequately excluded. The serum-alkaline-phosphatase was raised in 4 of the 5 cases with jaundice: in 1 it was not estimated. The serum-cholesterol was normal in all cases. 2 of the 3 cases with pericholangitis and bile stasis had a reversed albumin/globulin ratio and an abnormal zinc-sulphate-turbidity reaction. The authors felt that this "probably indicates a transition stage toward primary (cholangiolitic) cirrhosis".

Kimmelstiel et al. (1952) reviewed 93 necropsies in cases of ulcerative colitis and found interlobular hepatitis in 9. The pathological picture of this lesion corresponds essentially to a pericholangitis. In only 1 case had there been clinical evidence of liver disease.

Warren and Sommers (1949) found 2 cases of pericholangitis with fibrosis among 60 cases of ulcerative colitis coming to necropsy; and in a similar series of 91 necropsies Jones et al. (1951) found portal inflammation in 5 cases, portal fibrosis in 3, and pericholangitis in 1 case.

Without biliary obstruction pericholangitis may be attributed to hypersensitivity (as in drug hepatitis), viral infection, an autoimmune mechanism, or portal bacteræmia.

In our cases, drug hepatitis and serum or transfusion hepatitis have been excluded. Infectious hepatitis cannot be completely ruled out, and such infection has been known to progress to biliary cirrhosis (Watson and Hoffbauer 1946); but the long history of liver disease, its episodic nature, the absence of known contact, and the protracted episodes of jaundice make this diagnosis unlikely. Nor did our clinical, biochemical, and histological findings support it.

That these cases could represent a "collagen" disorder must be considered. The lupus-erythematosus (L.E.) cell was not found in the 4 patients in whom it was sought and none developed other features suggestive of a systemic collagen disorder. Gray et al. (1958) have described cases of active cirrhosis and ulcerative colitis, some with elevation of serum-alkaline-phosphatase. The L.E. cell, however, was found in several of these, and in most cases there was other clinical and laboratory evidence to support the diagnosis of systemic lupus erythematosus. Ross et al. (1956) have reported a raised serum-alkaline-phosphatase in systemic lupus erythematosus with hepatic involvement.

Portal bacteræmia in ulcerative colitis has been recently demonstrated by Brooke and Slaney (1958), who found intestinal bacteria in samples of blood taken from the veins draining the colon. They did not find portal bacteræmia when the operation was being performed for diseases other than ulcerative colitis. In the patients with portal bacter-

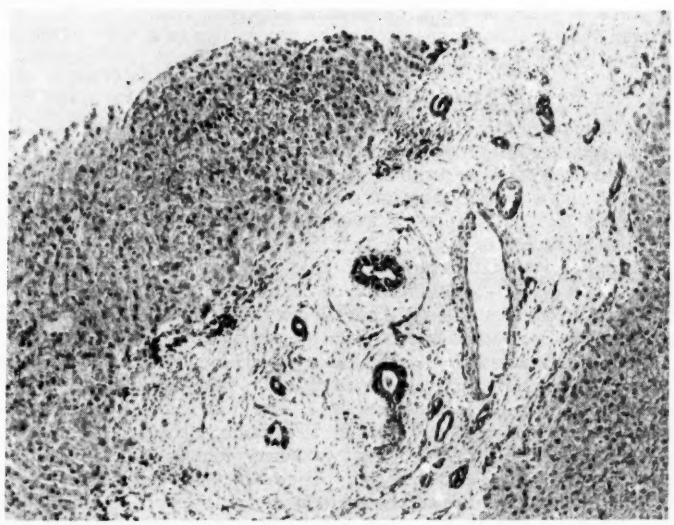

Fig. 2—Photomicrograph showing œdema of the portal tract with inflammation.

æmia there was no clinical evidence of liver disease; but liver biopsy in 1 of them showed peripheral lobular degeneration and fatty replacement " in the vicinity of the afferent venules ". Brooke and Slaney's study was prompted by a case of transient jaundice after colectomy for ulcerative colitis. We have taken samples from the venous drainage of the colon in 3 cases of ulcerative colitis coming to surgery.

Streptococcus fæcalis was isolated from the first, *Escherichia coli* from the second, and no organism from the third—a patient who had received preoperative treatment with broad-spectrum antibiotics.

That portal bacteræmia can lead to pericholangitis and cirrhosis was first suggested by Weaver in 1900. He produced the lesions in guineapigs by the intraperitoneal injection of a culture of *Esch. coli*. In 1901 Hektoen produced similar hepatic lesions in animals with a diphtheroid organism.

MacMahon and Mallory (1931) point out the difficulties in interpreting such results because the response differs in different species. They found that in rabbits the hæmolytic streptococcus could produce focal hepatic necrosis and fibrosis, and that clinical cases of streptococcal infection coming to necropsy showed an acute hepatic inflammation. This could lead to changes resembling healed acute yellow atrophy. MacMahon (1931) had earlier described 5 cases of " uncomplicated infectious cirrhosis " selected from a necropsy series of biliary cirrhosis. Evidence of biliary obstruction was absent in these 5: the pathological picture was that of a pericholangitis with a variable degree of connective-tissue and bile-duct proliferation in the portal areas. In 2 a colon bacillus in pure culture had been isolated from the liver; in 1 the lesions had not passed the acute inflammatory stage. Of the remaining 3, 2 showed old healed lesions without demonstrable bacteria, and 1 showed bacteria within the chronic lesions. MacMahon and Mallory felt that the likely mode of infection was by way of the unobstructed bile-ducts; but they could not exclude a blood-stream or lymph-borne infection.

Stewart and Jones (1941) described similar hepatic lesions in rats suffering from ulcerative cæcitis, a spontaneous disease in this animal.

In 1952 Kleckner et al. and Kimmelstiel et al. suggested that their cases of pericholangitis could have been due to portal toxæmia or portal bacteræmia associated with ulcerative colitis. Some appeared to be progressing to a primary biliary (cholangiolitic) cirrhosis (Kleckner et al. 1952).

Summary and Conclusions

We have presented 11 cases in which chronic ulcerative colitis was associated with serum-alkaline-phosphatase levels above 50 King-Armstrong units. 7 of these were shown to have a pericholangitis without obstruction to the biliary tree, and of these 2 developed cirrhosis and 1 a cholangiocarcinoma.

These cases, as well as reports of other observers, lead us to believe that an intermittent or continuous portal bacteræmia complicates some, if not all, cases of ulcerative colitis. This bacteræmia may result in a pericholangitis.

Though clinical and biochemical evidence of liver disease is often absent at first, repeated insults may produce pericholangitis and fibrosis at a time when the colitis has become mild and chronic. If sufficiently continuous and severe, they can lead to biliary cirrhosis; and there is some evidence that pericholangitis may precede the development of cholangiocarcinoma (Popper and Schaffner 1958).

Liver-function tests should be carried out in patients suffering from non-specific ulcerative colitis, particular attention being given to the levels of serum-alkaline-phosphatase and bromsulphalein retention. If there is clinical or biochemical evidence of liver disease, needle biopsy of the liver should be performed.

Conversely, in patients presenting with the clinical picture of liver disease, as described in this paper, ulcerative colitis should be sought.

The observation that pericholangitis may be reversible in the early stages raises two questions. First, should such patients have a total proctocolectomy because of the pericholangitis? Second, if colectomy is not performed, should they receive long-term treatment with sulphonamides or broad-spectrum antibiotics?

We are grateful to Dr. V. J. McGovern (histopathologist) and Prof. C. R. B. Blackburn for their encouragement and advice; to Mr. S. Woodward Smith, of the department of Medical Artistry, University of Sydney, for the photomicrographs; to the Fairfax Institute of Pathology for biochemical estimations and histological preparations; and to the honorary medical staff of the Royal Prince Alfred Hospital for making their patients available for investigation.

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INTESTINAL ABSORPTION OF LIVER-BOUND RADIOVITAMIN B_{12} IN PATIENTS WITH PERNICIOUS ANÆMIA AND IN CONTROLS

P. G. REIZENSTEIN
M.D.
OF THE DEPARTMENT OF INTERNAL MEDICINE AND GUSTAF V RESEARCH INSTITUTE, KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

W. NYBERG
M.D.
OF THE DEPARTMENT OF INTERNAL MEDICINE, CENTRAL HOSPITAL, VASA, FINLAND

IN Nature and in human food, vitamin B_{12} occurs as non-dialysable complexes but not as crystalline cyanocobalamin. The intestinal absorption in man of such natural vitamin-B_{12} complexes has been little studied (Coates et al. 1955, Latner 1958a and b, Nyberg and Reizenstein 1958). For this reason we have compared the intestinal absorption of non-dialysable, labelled vitamin-B_{12} contained in liver with that of solutions of crystalline radio-B_{12}.

Material

9 healthy volunteers aged 17–38 years (7 male and 2 female) and 2 patients with irrelevant diseases (hypoplastic anæmia and mediastinal tuberculosis) served as controls.

TABLE I—CLINICAL DATA OF PERNICIOUS-ANÆMIA PATIENTS

Case no.	Sex and age	B_{12}-absorption (Schilling test) (% of given amount)		Serum vitamin B_{12} conc. ($\mu\mu$g/ml.)	Megaloblastic bone-marrow	Histamine-fast gastric achlorhydria	Hæmoglobin (g. per 100 ml.)		Red cells (million per c.mm.)		Reticulocytes (per 1000 red cells)	
		Free B_{12}	B_{12} + intrinsic factor				Before liver feeding	After liver feeding	Before liver feeding	After liver feeding	Before liver feeding	After liver feeding
3	M.60	2		16		+	7·0	9·1	<2·34	3·17	12	20
7	F.67	1		*	+	+	*					
8	M.70	0		21	+	+	4·8	7·4	1·43	2·20	8	111
9	F.59	0	22	30		+	†				2	2
16	M.78	3		*			*					
17	F.41	2	15	45	+	+	8·8	8·9	2·5	2·6		
18	F.71		18	54	+		9·6	8·9	2·1	2·0	2	9
19	F.70	9		95	+	(+)‡	8·8	9·6	2·3	2·7	13	6
20	F.70	5	19	*	+§	+	*					
21	M.73	2		*	−	+	*					

Empty spaces = test not performed.
* B_{12} injection before admission.
† Blood-transfusions given during experiment.
‡ Tubeless analysis ('Diagnex').
§ In 1952.

Case 3, 7, 8, 9, 17, 18—Pernicious anæmia.
Case 16—Pernicious anæmia + generalised arteriosclerosis + gastric carcinoma + myocardial infarction.
Case 19—Pernicious anæmia + anal fissure + vertebral fract.
Case 20—Pernicious anæmia + diabetes mellitus + thrombosis (left leg).
Case 21—Pernicious anæmia + gastrectomy (cancer 1946) + œsophageal varices (normal liver-function tests).

The anæmia patient had a normal vitamin-B_{12} absorption, measured by the Schilling test as described previously (Reizenstein 1959a). Unfortunately, no Schilling test was performed in the tuberculosis patient; data including this patient are therefore in parentheses (table II).

10 patients with defective vitamin-B_{12} absorption are described in table I. None of them had clinical or laboratory signs suggesting any reasons for the defective vitamin-B_{12} absorption other than lack of intrinsic factor (I.F.). In 4 (nos. 9, 17, 18, 20) I.F. normalised the absorption of vitamin B_{12}. For the sake of simplicity, all these patients are called pernicious anæmia (P.A.) patients. 6 of the P.A. patients were in relapse (nos. 3, 8, 9, 17, 18, 19), all showing a typical hæmatological response after parenteral vitamin-B_{12} treatment was started.

Methods

Preparation of Liver

^{60}Co-labelled vitamin B_{12} (Merck) was administered parenterally to a pig and a calf as described elsewhere (Reizenstein 1959b). At slaughter, the pig liver contained radioactivity corresponding to 6 mμg. of the injected radiovitamin per gramme wet weight and a total of 560 mμg. of vitamin B_{12} per g. as assayed with *Euglena gracilis* and *Lactobacillus leichmanni* 313 ATCC 7830 as described elsewhere (Reizenstein 1959b). The corresponding figures for calf liver were 9 and 350 mμg. per g. Cases 15, 17, and 21 received calf liver; pig liver was given to all others.

Weighed samples of raw ground liver were spiced with tomato ketchup (Heinz), onion, salt, and pepper, prepared in weighed cardboard containers and stored at about −25°C. The liver samples, freshly thawed, were usually served to the patients on a sandwich immediately before a meal. All persons were either watched while eating or else their plate was inspected immediately afterwards. Remainders and the cardboard containers were weighed, and the amount of liver eaten was calculated.

Control Samples of Crystalline Vitamin B_{12}

In order to let each person serve as his own control, 17 persons drank a solution of crystalline radiovitamin B_{12} containing amounts comparable to those given in liver (tables II and III). Usually this solution was given immediately before a meal. The time interval between the two feedings was at least eight days.

Absorption Measurement

For seven to eleven days after each isotope administration all fæces were collected in plastic containers. Each person delivered the same number of fæces collections after eating liver as after eating B_{12}. In order to ensure quantitative fæces collection, the nursing staff and each subject were carefully and repeatedly instructed. In a few cases daily samples were obtained, but in most cases the fæces were pooled, digested with nitric acid, and concentrated by evaporation. Usually, the statistical error in scintillation counting was 2% of the original value, but in cases 12 and 14 it was up to 5%.

In addition to measuring the fæcal excretion, a few attempts were made to judge the absorption by the hæmatological response after the administration of liver and by measuring the radioactivity of serum samples. The statistical errors in the measurements of serum radioactivity were high (8–32% of the original values).

Results

Controls.—From an average of 22 μg. of liver-bound B_{12} eaten, 30% or 6 μg. was retained, as compared to 17% or 3 μg. retained from an average of 37 μg. crystalline B_{12} (table II). Half of the controls retained more of the

TABLE II—RETENTION OF RADIOACTIVITY AFTER ORAL ADMINISTRATION OF LIVER-BOUND AND CRYSTALLINE RADIO-B_{12} IN CONTROLS

Control no.	Liver-B_{12}			Cyanocobalamin		
	μg. administered	μg. retained	% retained	μg. administered	μg. retained	% retained
1	28	13	48	40	7	18
2	27	15	54	40	0·4	1
4	29	4	15	50	0·7	1
5	28	7	25	50	0·5	0·9
6	30	7	21	50	0·3	0·6
10	26	9	36	40	5	12
11	26	3	11	40	6	14
12	15	4	28	15	3	20
13	27	4	16	..	..	..
(14	5	2	34)	..	..	..
15	2	1	38	4	3	82
Means ± SE	24 (22	7±1·4 6±1·4	29±4·5 30±4·2)	37	3±0·9	17±8·3

Values in parentheses include case 14. Fractions of μg. given only for values less than 1 μg.

TABLE III—RETENTION OF RADIOACTIVITY AFTER ORAL ADMINISTRATION OF LIVER-BOUND AND CRYSTALLINE RADIO-B_{12} IN PERNICIOUS-ANÆMIA PATIENTS

Case no.	Liver-B_{12}			Cyanocobalamin		
	μg. administered	μg. retained	% retained	μg. administered	μg. retained	% retained
3	33	23	69	..	..	..
7	14	6	40	20	<4	<21*
8	35	16	45	50	2	4
9	35	32	91	40	3	9
16	27	4	15	28	0·6	2
17	3	0·6	18	4	0·05	1·2
18	9	3	36	5	0·7	13
19	27	5	19	28	4	13
20	10	0·2	2	5	0·06	1
21	3	0·7	21	4	0·02	0·4
Means ± SE	20	9±3·5	36±8·6	20	2±0·6	7±2·4

* One 24-hour fæces collection lost.

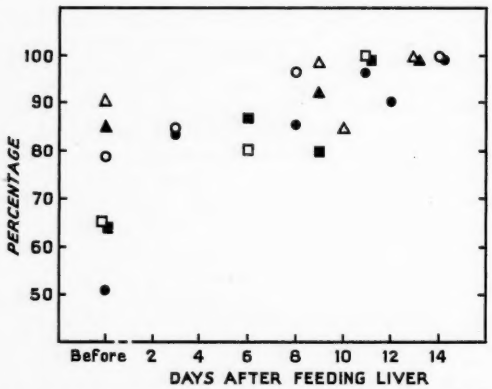

Fig. 1—Increase in blood values after feeding liver to pernicious-anæmia patients.

The figure describes the increase in hæmoglobin (empty symbols) and red cells (filled symbols), expressed on the ordinate in per cent of the final values attained by the patient during the period where all therapy except the single dose of 10–60 g. raw liver could be withheld.
○: case 3 □: case 8 △: case 19
The increase in red cells is 15–48%, in hæmoglobin 10–35% of the final value.

liver-B_{12} than of the crystalline B_{12}. The significances of the differences found are given in table IV.

Pernicious anæmia—From an average of 20 μg. of liver-bound B_{12}, 36% or 9 μg. was retained, as compared to 7% or 2 μg. after the administration of about 20 μg. of crystalline vitamin B_{12} (table III). In each case the apparent absorption of liver-B_{12} was larger than that of crystalline B_{12}. The differences, whether expressed in μg. or in per cent, were statistically significant (table IV).

5 of the 10 cases of P.A. (cases 3, 8, 17, 19, 21) had received no treatment before or during the present experiments. They could therefore be employed to check the values obtained for absorption by comparing these values with the hæmatological response after the single small liver dose. An evident increase in blood values was found in 3 patients (fig. 1, table I). In agreement with earlier studies of oral treatment of P.A. (Spies et al. 1949, Meyer et al. 1950), only 1 patient showed reticulocytosis. Naturally, complete remission was not seen after a single oral liver dose.

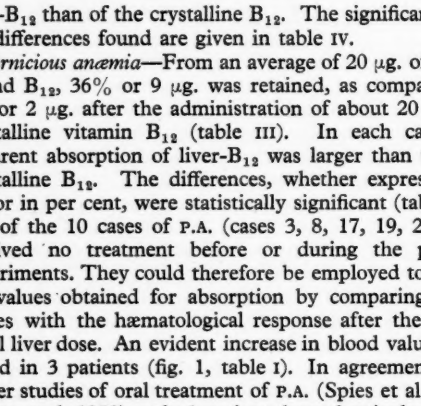

Fig. 2—Connection between the amount of liver-bound vitamin B_{12} absorbed as estimated from the hæmatological response and that obtained from fæcal excretion measurements.

The regression coefficient of log. y upon log. x is $0{\cdot}88 \pm 0{\cdot}32$.

In all 5 patients a rough estimate of the amount of B_{12} absorbed was made by aid of the increase in the red-blood-cell count (R.B.C.) and the graph constructed by Campbell and McLaughlan (1956). Fig. 2 shows the expected relation between the amount of B_{12} absorbed as estimated from the hæmatological response and that measured by aid of the fæcal excretion.

The coefficient of correlation was 0·87. In 4 patients (cases 18–21), between 6 and 17% of the total radio-activity given in liver was calculated to be present in the plasma (table V).

Discussion

The Method

There is probably no better way at present to measure the intestinal absorption of radiovitamin B_{12} than the laborious fæcal excretion method. Nevertheless, this method cannot be claimed to be wholly quantitative. It is possible that some fæcal material may be lost and also that some radioactivity may be excreted after the fæces collection has been terminated. Since this source of error was common to the experiments with liver-bound B_{12} and those with cyanocobalamin, it is unlikely to have influenced the statistically significant difference. Moreover, there are the following indications that the collection of twenty-four-hour fæces portions for seven to eleven days is an adequate method of measuring vitamin B_{12} absorption.

TABLE IV—STATISTICAL SIGNIFICANCE OF THE MEAN DIFFERENCES BETWEEN THE ABSORPTION OF LIVER-BOUND AND CRYSTALLINE RADIOVITAMIN B_{12}

Group of subjects	Differences between	Differences between log values*	
		Mean ± S E	Significance of deviation from zero
Controls	μg. liver-bound and μg crystalline B_{12}	$0{\cdot}65 \pm 0{\cdot}22$ n=9	$0{\cdot}02 > P > 0{\cdot}01$
	% liver-bound and % crystalline B_{12}	$0{\cdot}58 \pm 0{\cdot}25$ n=9	$0{\cdot}05 > P > 0{\cdot}02$
Pernicious anæmia	μg. liver-bound and μg crystalline B_{12}	$0{\cdot}75 \pm 0{\cdot}16$ n=9	$0{\cdot}005 > P$
	% liver-bound and % crystalline B_{12}	$0{\cdot}59 \pm 0{\cdot}12$ n=9	$0{\cdot}005 > P$

* The logarithmic transformation was performed in order to normalise the skew distributions.

TABLE V—APPROXIMATE AMOUNT OF RADIOACTIVITY CONTAINED IN PLASMA 1–6 DAYS AFTER ORAL ADMINISTRATION OF LIVER-BOUND RADIOVITAMIN B_{12}

Case no.	Days after liver administration	Approximate percentage of radioactivity eaten contained in total plasma volume*
18	6	17
19	1	6
20	5	7
21	1	16

* Plasma volume in megaloblastic anæmia estimated to be approximately 116% (Hallberg 1955) of normal plasma volume or $1{\cdot}16 \times 41$ ml. per kg. body-weight (Geigy 1956).

The fæcal excretion pattern after oral radiovitamin administration has been studied by Halsted et al. (1956) in 340 persons of whom 70% excreted no appreciable radioactivity later than three or four days after eating. In 4 of the present persons (nos. 15–17, 19) a twenty-four-hour fæces sample obtained on the eighth day after administering liver contained between 0·3 and 0·5% of the total radioactivity given. Finally, the present values for intestinal absorption (3 μg.) are compatible with earlier values (1·5 μg., Glass 1954). Glass' absorption values

were calculated from the radioactivity over the liver projection, and the difference between 1·5 and 3 μg. may be due to the different methods.

Unfortunately, several persons did not receive identical amounts of liver-B_{12} and crystalline B_{12}. Since relatively less of large doses than of small ones is absorbed (Glass 1954) this difference could affect the difference between percentage absorptions (Gräsbeck et al. 1958). It could not, however, affect the differences between the absolute amounts in μg. of B_{12} absorbed. Moreover, even in 8 of the 9 cases where the amounts of crystalline B_{12} were equal to or smaller than those of liver-B_{12} (cases 7, 12, 16–18, 20, 21, 27), more was retained of the latter. On the whole, the greater absorption of liver-bound B_{12} can be seen over the whole dose-range employed.

Glass (1958) has demonstrated that after the administration of radiovitamin B_{12} most of the liver radioactivity represents vitamin B_{12}. However, Smith (1959) recently observed that solutions of labelled cyanocobalamin sometimes lose microbiological activity during storage. It is believed that this results from the interaction of radiation-induced reactive groups with the cyanocobalamin molecules. Since in the present study the radioactivity concentration was very low, present in liver instead of in solution, and at a temperature of −25°C, this effect is unlikely to be of major importance. For this reason, the radioactivity has been calculated as vitamin B_{12}. The fact that the hæmatological response appeared to be greatest when most of the radioactivity was absorbed (fig. 2) would also seem to indicate that the radioactivity represents B_{12}. However, this comparison could be made in 5 cases only.

Results

The relatively high radioactivities found in the serum seem to indicate that the radioactivity not excreted was really absorbed and not, for example, retained in the intestinal wall.

In the present experiments, there was apparently a (suboptimal) hæmatological response after a single dose of only about 60 g. raw liver (figs. 1 and 2, table II). This may be compatible with the smallest daily amount of (cooked) liver, which was tested and which was found to give a definite hæmatological response in pernicious anæmia in the days of oral liver treatment (60–80 g., Minot et al. 1928). However, according to the present studies, similar amounts of raw liver seem to enable considerably more vitamin B_{12} to be absorbed per day than 1 μg., which is the minimum daily amount of injected B_{12} giving a hæmatological remission (Bethell 1948). There are indications that injected B_{12} behaves differently from absorbed B_{12} (Chow et al. 1950, Meyer et al. 1950, Ungley 1950, Conley et al. 1951, Rosenblum et al. 1952, Johnsson and Berger 1958, Reizenstein 1959b), and such differences may explain the apparent disagreement between the minimum effective amounts of absorbed (liver-bound) and injected (free) B_{12}. On the other hand, it has not been definitely proved that all the liver radioactivity absorbed represents B_{12}.

With these reservations in mind the question why liver-B_{12} seems to be absorbed more easily than crystalline B_{12} can be discussed. It is possible that liver—unlike solutions of crystalline B_{12}—stimulates gastric secretion, or that it influences the rate of intestinal passage. However, it has been demonstrated that the administration of cyanocobalamin in connection with a meal limits rather than enhances B_{12} absorption (Gräsbeck et al. 1956), and the administration of radiovitamin B_{12} in delayed-release capsules does not seem to facilitate absorption either (Johnsson and Berger 1958). Besides, most of the present subjects received crystalline B_{12} immediately before a meal. Nevertheless, such factors may be of importance at least in the controls.

It is probable (Gräsbeck 1956), although not quite certain (Williams et al. 1954, Latner and Merrills 1956, Latner 1958b), that intrinsic factor binds vitamin B_{12}. Under the present experimental conditions, both the microbiological activity and the radioactivity in the liver were bound in the sense that they were undialysable (Reizenstein and Nyberg 1958, Bolinder, Callieri, and Reizenstein, unpublished). It is quite possible that liver-B_{12} occurs in the form of a B_{12}-peptide complex (Hausmann and Mulli 1952, Wijmenga et al. 1954, Hedbom 1955) loosely associated and precipitated together with protein (Pitney et al. 1955, Reizenstein and Nyberg 1958). Whether or not the association of a cobalamin with a peptide explains the apparent ease with which it is absorbed by patients with pernicious anæmia remains to be demonstrated.

I.F. is generally considered to be indispensable for the physiological absorption of B_{12}. However, if the present results are confirmed by further experiments, it is possible that there are really forms of vitamin B_{12} which may be absorbed by patients with pernicious anæmia in the absence of intrinsic factor. There seem to be no previous absorption studies demonstrating this. It is possible that the effect of oral liver treatment is not only due to the massive B_{12} dose or the folic-acid content of liver, but to the form in which B_{12} occurs. If this is so, then the role of the stomach and of I.F. in vitamin-B_{12} absorption certainly needs to be more clearly defined (*Lancet* 1958), perhaps by studying the function of I.F. together with naturally occurring B_{12} complexes.

At present the oral maintenance therapy of pernicious anæmia patients with B_{12} intrinsic-factor combinations is unsatisfactory (Berlin et al. 1958, Killander 1958). If liver contains vitamin B_{12} in an absorbable form, it may be worth ascertaining whether or not such preparations are more advantageous therapeutically.

The maximum amount of cyanocobalamin absorbed by healthy human beings after a single oral dose is, on the average, 1 μg. (Mollin 1959)—the same as the minimum effective daily parenteral B_{12} dose (Bethell et al. 1948). Consequently, this has been considered to be a suitable daily maintenance dose. In the present study, considerably larger amounts of liver-B_{12} seemed to be absorbed. If it could be shown that some of the bound B_{12} as it occurs in food were more readily absorbed than cyanocobalamin, this would justify a reconsideration of the normal requirements of vitamin B_{12} (Gräsbeck et al. 1958).

Summary

The intestinal absorption of radioactivity after the oral administration of liver containing labelled vitamin B_{12} was compared with the absorption of crystalline radiovitamin solutions. Both controls and pernicious-anæmia patients apparently absorbed more of the liver-B_{12}. The hæmatological response after eating liver was greatest when most radioactivity was absorbed. After feeding liver, some 10% of the radioactivity administered was calculated to be present in the plasma. These findings are critically reviewed and their possible therapeutic implications are discussed.

Dr. R. Gräsbeck and Dr. B. Åberg helped with the animal

experiments during the initial phase of the present study. Helpful and constructive criticism was offered by Dr. E. Lester Smith and Prof. H. Lagerlöf. Mr. N. Kulsdom gave skilled technical assistance. Generous support was received from the Astra Pharmaceutical Co., the Juselius Foundation, and the Finnish Medical Society.

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GLUTEN-INDUCED ENTEROPATHY

THE EFFECT OF PARTIALLY DIGESTED GLUTEN

A. C. FRAZER
M.D. Birm., D.Sc., Ph.D. Lond., F.R.C.P.
PROFESSOR OF MEDICAL BIOCHEMISTRY AND PHARMACOLOGY

R. F. FLETCHER
M.B., B.Sc. Birm., M.R.C.P.
UNIVERSITY RESEARCH FELLOW

CONSTANCE A. C. ROSS
M.D. Glasg.
PREVIOUSLY UNIVERSITY RESEARCH FELLOW

B. SHAW
Ph.D. Lond.
LECTURER

H. G. SAMMONS
Ph.D. Birm.
LECTURER

R. SCHNEIDER
M.D. Berlin, M.R.C.P., F.R.C.P.E.
LECTURER

From the Department of Medical Biochemistry and Pharmacology, University of Birmingham, and the Metabolic Unit, Little Bromwich General Hospital.

MOST children with cœliac disease and many adults with idiopathic steatorrhœa have disordered function of the small intestine (" enteropathy ") due to their inability to tolerate dietary wheat gluten (Dicke 1950, Anderson et al. 1952, Weijers and van de Kamer 1953, Anderson et al. 1954, Ross et al. 1955). Treatment with a gluten-free diet has a beneficial effect in such patients; reintroduction of gluten is deleterious. Complete acid hydrolysis of gluten makes it non-toxic to children with cœliac disease (Weijers and van de Kamer 1953, Alvey et al. 1957).

The object of this study was to find out whether the deleterious effect of wheat gluten in patients with gluten-induced enteropathy was modified by digestion of the gluten with pepsin and trypsin. The digestion stopped short of complete hydrolysis, and the resultant products were tested in gluten-intolerant patients. This work has been previously outlined (Shaw et al. 1955, Frazer 1957).

Materials and Methods

Wheat gluten.—The starting material used was commercial gluten extracted from flour milled from Canadian hard red spring wheat, without treatment with food additives or improvers. This is toxic to patients with gluten-induced enteropathy.

Pepsin.—The pepsin was a crystalline preparation derived from pig gastric mucosa (Armour Laboratories).

Trypsin.—The trypsin was a crystalline preparation from bovine pancreas containing less than 50% by weight of magnesium sulphate (Armour Laboratories).

Enzymic Hydrolysis of Wheat Gluten and Preparation of Fractions

Gluten 100 g. and pepsin 0·5 g. were added to 1 litre of *N*/10 HCl (resultant pH 1·8) and digestion was carried out at 37°C with continuous stirring for four hours. After adjustment of the pH to 7·8 with about 100 ml. of *N*.NaOH, trypsin 0·5 g. was added, and the digestion was continued under the same conditions for a further four hours. The mixtures at I and II (table I) were not examined in detail. The addition of about 50 ml. of *N*.HCl to mixture II until the pH was 4·5 gave a precipitate (fraction VI), which accounted for 20–25% by weight of the original gluten, and had a nitrogen content of 5·4%. The precipitate was removed by centrifugation at 2500 r.p.m., and the supernatant fluid (fraction III) was lyophilised. Some of fraction III was then dialysed against distilled water across a ' Cellophane ' membrane at 4°C for forty-eight hours, yielding fractions IV and V, which were 66% and 33% by weight respectively of fraction III. Fraction IIIA was obtained by autoclaving fraction III in solution at pH 7·8 and 120°C for twenty minutes, which caused precipitation of 3–5% by weight. Analytical data for gluten and fraction IIIA are shown in table II.

Characterisation of Fraction III

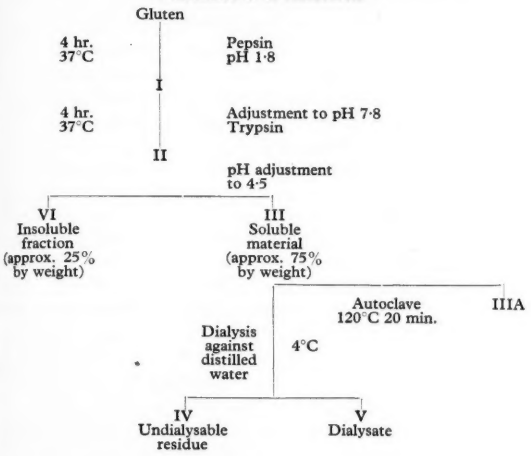
Gluten is a mixture of proteins which have never been completely separated or characterised. Gluten itself is largely water-insoluble, whereas fraction III is water-soluble, in the presence of salts. This change in physical properties, and the use of ultraviolet spectrophotometry (Smith 1955) show that the gluten had been digested.

Since fraction III was obtained from a heterogeneous material, characterisation of its components is difficult. Ultrafiltration, however, indicated that about 66% of the fraction was material with a molecular weight below 15,000, and that about 8% was free aminoacids, as judged by the ion-exchange technique of Partridge (1952). Investigation by paper chromatography, paper electrophoresis, dialysis, and precipitation with trichloracetic acid have all shown fraction III to be a complex mixture, not identical with the original gluten. Further attempts to define the components are in progress.

Acid hydrolysis of both fraction III and gluten, followed by qualitative paper chromatography, have shown that all the aminoacids present in gluten were in fraction III. The proportion of amide nitrogen to total nitrogen was 22% in gluten, and 23% in fraction III, which indicates no significant deamidation of glutamine and asparagine residues as a result of peptic/tryptic digestion.

The antigenic properties of gluten, fraction III, and fraction IIIA were tested, using isolated guineapig intestine from an animal sensitised to gluten. Gluten and fraction III showed a positive response, with tachyphylaxis; fraction IIIA was negative.

TABLE I—SCHEME OF ENZYMIC DEGRADATION OF GLUTEN, AND PREPARATION OF FRACTIONS



Clinical Testing of the Fractions

Tests were made in six patients who had had steatorrhœa before a gluten-free regime was started.

Fæcal fatty acid was measured daily, by a method based on that of van de Kamer et al. (1949). Pancreatic enzymes were studied as described by Anderson et al. (1952) and Sammons et al. (1956). Both flocculable and non-flocculable barium-sulphate preparations were used for small intestinal radiographs (Frazer et al. 1949, Ardran et al. 1950, Astley and French 1951). The chylomicrograph technique of Frazer and Stewart (1939) was used. For oral glucose-tolerance tests, blood-sugar was estimated by the Hagedorn-Jensen method. In one patient, a xylose-tolerance test was carried out (Brien et al. 1952). In the more recent studies these methods were slightly modified from the above; they will be described elsewhere.

The details of the patients and results of the diagnostic investigations are listed in table III.

Cases 1–3 and 6 were typical of cœliac disease in childhood. Case 4 had a long history of recurrent anæmia, but had only recently developed diarrhœa. Case 5 presented with symmetrical dwarfism, iron-deficiency anæmia and pale stools; this patient has grown rapidly on a gluten-free diet (Frazer 1956). All the patients were treated effectively by a strict gluten-free regime (Fletcher and McCririck 1958).

TABLE II—COMPOSITION OF GLUTEN AND FRACTION III

—	Nitrogen*	Amide nitrogen*	Ash	Sodium	Chloride	Potassium
	(g. per 100 g.)					
Gluten ..	13·9	3·2	0·6	0·008	0·035	0·006
Fraction IIIA	15·5	3·4	7·9	3·6	5·6	0·25

* Calculated on an ash-free basis.

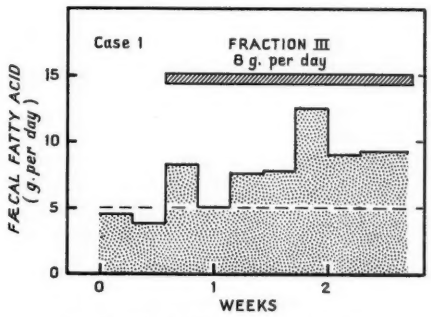


Fig. 1—Effect of fraction III in case 1.

In several patients (we should have preferred in all) gluten was reintroduced into the diet, and shown to be deleterious by a subsequent rise of fæcal fat.

Fraction feeding tests were carried out during a later admission when the patients had been on a gluten-free regime for several months, and the fæcal fat had returned to normal, or near normal. Each fraction was fed, unless otherwise stated, in an amount proportional to 10 g. of gluten per day—e.g., 8 g. daily of fraction III, which formed 80% of the original gluten. This scheme avoided the risk of feeding excessive amounts of toxic material, and made a quantitative assessment of the deleterious effect possible. The patients were kept on a gluten-free diet throughout, and the daily dose of the fraction was mixed with food at one or several meals. Occasionally the fraction was given in a drink, and once it was mixed with butter alone. A rise in fæcal fat was taken as objective evidence of toxicity; subjective changes were also noted.

Results

CASE 1.—Positive response to fraction III. The fæcal fat levels are shown in fig. 1. Anorexia developed after thirteen days.

CASE 2.—Positive response to fractions IV and V recombined to give a mixture equivalent to fraction III. 8 g. per day of this mixture was fed, and the fæcal fat levels are shown in fig. 2.

CASE 3.—Positive clinical response. A single dose of

TABLE III—DETAILS OF PATIENTS AND RESULTS OF DIAGNOSTIC INVESTIGATIONS

Case no.	Sex	Initial status: Age (yr.)	Fæcal fat (g. per day)	Pancreatic enzymes	Glucose tolerance	Xylose tolerance	Chylomicrograph	Radiographs	Status: After treatment with a gluten-free diet	Response to gluten
1 (92645) • ..	M	7	11·5	N	N		A+++	A	N	Not done
2 (79814) • ..	M	8	15·1		A+		A+		N	Not done
3 (L/40)	F	3	11·7	N			A+	A	N	Not done
4 (G/37)	F	51	14·0		A+	A++	A+++	A	N	+
5 (T/77)	F	14	10·0	N	N		A+++	A	N	+
6 (54283) • ..	F	4	7·9	N			A+		N	+
					Maximum increment	Excretion	Maximum increment			
Normal	N		<5·0		>40	>20%	>120			
Abnormal ..	A+ A++ A+++				20–40 10–20 0–10	15–20 10–15 10	100–120 50–100 0–50			

• Birmingham Children's Hospital no.

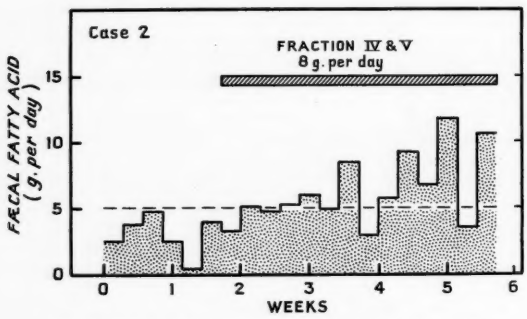


Fig. 2—Effect of fractions IV and V combined in case 2.

fraction IIIA on the first day was followed two hours later by vomiting. 3 g. were given daily for the next two days. The child was then fractious for two days, and no test material could be given. Over the next twelve days an average of 3·7 g. was given daily. The fæcal fat did not rise, but the child was ill and anorexic, and lost 2·0 kg. in weight; further feeding was felt to be unjustified.

CASE 4.—Positive response. Fraction IIIA, further digested with hog's intestinal mucous-membrane extract, was given for two days in a dose of 8·0 g. daily; on the third day 4·3 g. of unmodified fraction IIIA was given. The fæcal fat levels are shown in fig. 3.

CASE 5.—Positive response to 5 g. of fraction IIIA mixed with 30 g. of butter. Some days later the same amount of dehydrated soup powder, mixed with 30 g. of butter, was given as a control. The fæcal fat figures are shown in fig. 4.

CASE 6.—Negative response to fraction VI at a level of 2·5 g. daily for twenty-six days. There was no change in fæcal fat, and no subjective changes.

The results of these tests are summarised in table IV.

Discussion

Intolerance to wheat gluten is a major factor in the ætiology of the enteropathy observed in almost all children with cœliac disease and most adults with idiopathic steatorrhœa. We are here concerned with the investigation of the underlying cause of the deleterious effect of wheat gluten in these patients.

Our findings show conclusively that the chemical treatment of flour is not a necessary factor in producing deleterious effects in patients with gluten-induced enteropathy. All the materials we used were made from untreated flour. Furthermore, flour treated with more than ten times the commercial level of chlorine dioxide, when tested in a patient with gluten-induced enteropathy, was shown to be not more, and possibly slightly less, harmful than the same flour untreated (Anderson et al. 1952). One must conclude, therefore, that the deleterious effect of wheat flour in gluten-induced enteropathy is due to some property of untreated wheat gluten.

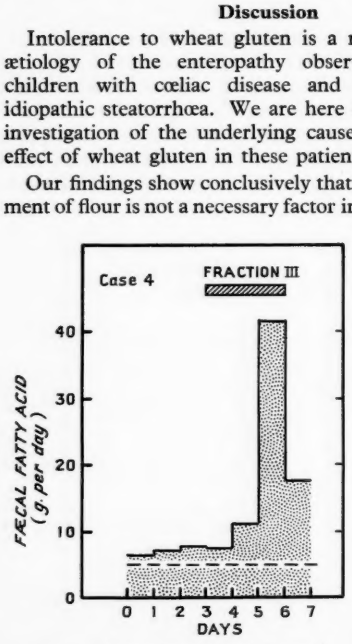


Fig. 3—Effect of fraction III in case 4.

Earlier evidence indicated that proteolytic activity in gastric and duodenal juice was within normal limits in patients with gluten-induced enteropathy. Enzymic degradation of gluten by pepsin and trypsin in vitro, with or without subsequent precipitation of residual protein by autoclaving, does not materially alter the deleterious effect of gluten in these patients. Krainick (1957) has shown that an ultrafiltration of a peptic/tryptic digest of gliadin was still toxic. These observations are compatible with the view that the harmful effect of the gluten is due to the presence of a peptide or some other fragment present in wheat gluten, which is not handled as effectively by patients with gluten-induced enteropathy as by normal people.

If the effect was due to antigens present in wheat gluten, a sufficient amount of residual protein might be present in the enzymic hydrolysate to affect a sensitised individual. Such a reaction was demonstrated with fraction III in gluten-sensitised guineapig intestine. However, the autoclaved product, fraction IIIA, no longer caused this reaction. Fraction IIIA appears to be as effective as fraction III in patients with gluten-induced enteropathy. The effect of the fraction IIIA cannot, therefore, be attributed to the presence of residual gluten in the enzymic hydrolysate acting as an antigen in a gluten-sensitive person. The possibility that breakdown products of gluten may have antigenic properties is still being studied.

TABLE IV—RESULTS OF FEEDING GLUTEN FRACTIONS TO THESE PATIENTS

Fraction	III	IIIA	IV and V	VI
Case 1	+			
Case 2			+	
Case 3		(+)*		
Case 4		+		
Case 5		+		
Case 6				0

+ = positive response.
0 = negative response.
* = clinical response only.

Work on the nature and metabolism of the deleterious agent continues.

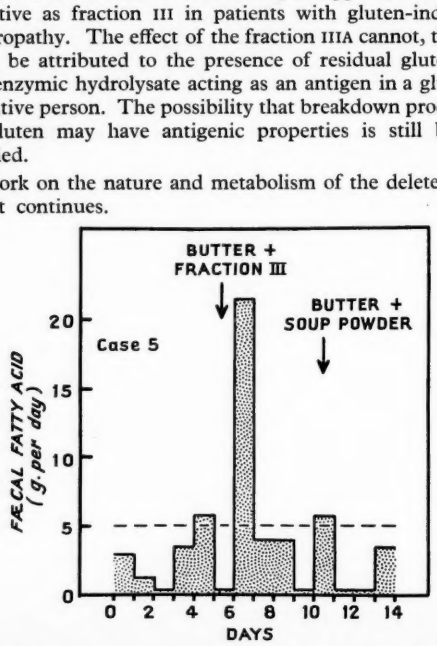


Fig. 4—Effect of butter and fraction III, and a control test, in case 5.

Summary

The preparation of products of enzymic (peptic/tryptic) degradation of wheat gluten is described. The wheat gluten used was untreated with additives or improvers.

The water-soluble product (fraction III) contained 66% ultrafiltrable material and 8% free aminoacids. This was autoclaved to yield fraction IIIA.

Gluten and fraction III had antigenic properties, giving a positive response in isolated intestine from guineapigs sensitised to wheat gluten; fraction IIIA was negative when similarly tested.

Fractions III and IIIA were tested in patients with gluten-induced enteropathy. They were equally deleterious, and did not appear to be less toxic than the gluten from which they were derived.

We are indebted to Prof. J. M. Smellie for referring cases 1, 2, and 6, to Dr. A. C. Crooke (case 5), and to Dr. R. D. Blachford (case 4); and to Professor Smellie also for research facilities at the Children's Hospital, Birmingham, in the early stages of this work. We are grateful to the sisters, the nurses, dietitians, and kitchen staff of the metabolic unit, Little Bromwich General Hospital, and to the sister and the nurses of ward 4 at the Children's Hospital for their help. We are indebted to Dr. O. C. Forbes for assistance with tests for antigenic activity. Much has been contributed by the technical staff in our research laboratory at the Children's Hospital, and in the laboratories at Little Bromwich General Hospital. Mr. G. Franklin gave valuable technical assistance in the preparation of the gluten fractions. The Energen Foods Co. provided supplies of wheat gluten.

The Medical Research Council and the Birmingham United Hospitals research fund provided financial support.

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DEXAMETHASONE

F. DUDLEY HART
M.D. Edin., F.R.C.P.
PHYSICIAN IN CHARGE OF THE RHEUMATISM UNIT

J. R. GOLDING
B.A., B.M. Oxon., M.R.C.P.
SENIOR REGISTRAR

GEORGE BROWN
M.B. Lond., D.Obst.
REGISTRAR

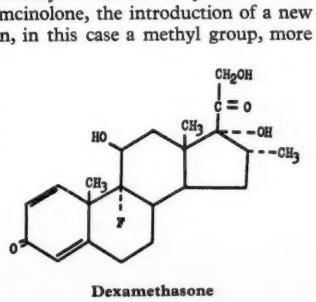
WESTMINSTER HOSPITAL, LONDON, S.W.1

IN the eleven years since Hench, Kendall, Slocumb, and Polley (1949) first described the clinical use of cortisone, a great deal of work has been done in modifying the cortisone molecule in an attempt to vary its clinical actions and diminish its so-called side-effects—i.e., the effects of overdosage (hypercortisonism). Fludrocortisone (Fried and Sabo 1953) proved to have 10 times the anti-inflammatory effect of hydrocortisone, while its influence on electrolyte and water metabolism was about 125 times greater (Borman et al. 1954, Liddle et al. 1954): apart from its external use in dermatology, it is now used only in adrenal-deficiency states because of this potent mineralocorticoid action (Garrod et al. 1955, Hart 1956). The unsaturated delta-1 derivatives of cortisone and hydrocortisone—prednisone and prednisolone—followed soon afterwards (Herzog et al. 1955, Bunim et al. 1955), the advantage over their predecessors lying essentially in diminished mineralocorticoid action at therapeutically effective doses. Soon afterwards methyl prednisolone appeared (Hogg et al. 1955) and triamcinolone (9α-fluoro-16-hydroxy-δ1-hydrocortisone) (Bernstein et al. 1956) followed; the addition of a hydroxyl group at C16 appeared to abolish the marked sodium-retaining effect of fluorine at C9 and this compound has even less sodium-retaining effect than prednisone and prednisolone (Freyberg et al. 1958). Patients treated on this substance had certain side-effects not noted with other steroids, such as postprandial flushing and muscle weakness (Dubois 1958, Freyberg et al. 1958, Hart, Golding, and Burley 1958, Williams 1959).

The approximate dose ratio, when it is used as an anti-inflammatory or "antirheumatic" agent, with these different substances is, in our experience, 25 mg. cortisone acetate=20 mg. hydrocortisone=5 mg. prednisolone or prednisone=4 mg. methylprednisolone or triamcinolone. There appears to be a considerable patient-to-patient variation, some doing better on one substance for a time, some on another. While it is useful to have a number of different steroid substances to change to, we think that the essential and main drawback to this form of therapy is the high incidence of gastroduodenal side-effects with all of the above-named substances. This may, in part at least, be due to a local gastric action, and possibly in part to aspirin also, for this complication is not commonly seen in idiopathic, as opposed to iatrogenic, Cushing's syndrome. All the other effects of hypercortisonism—moon-face, striæ, acne &c.—appear with all these substances, the incidence depending largely on dosage rather than on the particular substance used. The only practical differences which are apparent to the clinical worker are the side-effects noted above with triamcinolone and the varying sodium-retaining effects with the different substances. When therefore a newer substance, dexamethasone, appeared (Arth et al. 1959), we decided to compare it with prednisolone in the same way as we had previously compared triamcinolone with prednisolone (Hart, Golding, and Burley 1958), and prednisone and prednisolone with cortisone (Hart, Clark, and Golding 1955).

Chemistry and Pharmacology

Dexamethasone is 16α-methyl-9α-fluoro-Δ^1-hydrocortisone[1] (see figure). As with triamcinolone, the introduction of a new radical at the C16 position, in this case a methyl group, more than neutralises the sodium-holding effect of the fluorine at C9. Substituting a methyl for the hydroxyl group at C16 enhances the glucocorticoid or "anti-inflammatory" effect very considerably.



Dexamethasone

Bunim et al. (1958) found dexamethasone to have a longer

half-life after intravenous injection than hydrocortisone in the same group of normal human subjects. The same workers demonstrated a potent suppression of pituitary corticotrophin secretion and found that in patients with rheumatoid arthritis, 1–2 mg. a day of dexamethasone reduced the concentration of hydrocortisone in the plasma to zero within twenty-four hours, with diminution of circulating eosinophils and considerable decrease in urinary excretion of corticoids and 17-ketosteroids. In a typical patient, the hydrocortisone content of the plasma, which averaged 23 μg. per 100 ml. before treatment, was reduced repeatedly to zero within twenty-four hours and the average twenty-four hour output of urinary corticoids from 5·4 to 0·4 mg. In normal subjects they found that dexamethasone did not depress aldosterone activity. Using a high dosage of 6–10 mg. a day, Bunim et al. (1958) found a definite negative calcium balance; and this was confirmed by Slater et al. (1959).

The use of this obviously potent new substance has been already reported in rheumatoid arthritis by Bunim et al. (1958) and Boland (1958), and at a conference on its uses held last December in the United States (*British Medical Journal* 1959). We have set out to answer only one question: has dexamethasone any practical advantages over its predecessors in the treatment of rheumatoid arthritis?

Scheme of Trial

In each case dexamethasone was compared directly with the steroid previously administered (which in all cases but 2 was prednisolone), two tablets (1 mg.) of the former substance replacing one (5 mg.) of the latter—i.e., a dose ratio of 1/5 for dexamethasone/prednisolone. As in previous studies with prednisolone (Hart, Clark, and Golding 1955) and triamcinolone (Hart, Golding, and Burley 1958), the changeover to the newer substance was for a period of one to twenty-four weeks; the result was classed in favour of the new substance if improvement occurred on changing to it and deterioration on returning to the previous compound. Improvement was judged on the patients' own daily assessment of pain and stiffness, measurement of grip with a soft cuff inflated to 30 mm. Hg. on a sphygmomanometer, and finger swelling as measured by jeweller's rings (Hart and Clark 1951). In 6 cases the systemic index of Lansbury (Lansbury and Mueller 1956, Lansbury 1958) was also used; assessment by this method gave the same general results as by our own. Particular note was taken of aggravation or amelioration of dyspepsia.

Results

Rheumatoid Arthritis

Of these 30 cases, 17 were women. The patients were between 38 and 70 years of age, 7 patients being 60 or over. The disease had been present from one to eighteen years.

Nearly half of these patients had already received long-term steroids—cortisone, prednisolone, or triamcinolone. They were thus in an excellent position to assess subjectively any new steroid in an impartial way.

On the patients' own assessment dexamethasone was preferred in 12 cases, prednisolone was preferred in 12 cases, and the two were considered equal in 6 cases (see table). Grip improved on dexamethasone in 4 cases, deteriorated in 1, and was unchanged in 22; in 3 cases it was not assessed. Finger swelling improved on dexamethasone in 4 cases, deteriorated in 4, and was unchanged in 19; in 3 cases it was not assessed. Indigestion improved on dexamethasone in 2 cases and worsened in 3; in 9 dyspepsia was the same with either, in 16 it was absent with both drugs.

Erythrocyte-sedimentation rates were compared in 16 patients; there was a significant difference in only 1, a patient in whom the rate fell to normal with dexamethasone.

Systemic Lupus Erythematosus

In 3 cases there was nothing to choose between dexamethasone and prednisolone either on examination or on the patients' history. All were women, aged 22, 32, and 34.

EFFECT OF TREATMENT WITH DEXAMETHASONE COMPARED WITH THAT OF PREDNISOLONE

Case no.	Sex	Age (yr.)	Length of history (yr.)	Subjective pain and stiffness on dexamethasone (%)	Grip	Finger swelling	Indigestion	Comment
1	F	51	13	Much greater	Not done	Not done	Unchanged	Rapid deterioration on dexamethasone
2	F	59	14	100	Unchanged	Unchanged	Unchanged	Anginal pain less on dexamethasone. E.S.R. unchanged at 40
3	F	62	6	150	,,	,,	Much worse	E.S.R. normal on both
4	F	61	5	500	Not done	Not done	Worse	Normally mobile, confined to bed with dexamethasone
5	M	70	2	150	+20%	+14	Much worse	Hands improved, but generally much worse
6	M	56	10	100	Unchanged	Unchanged	Improved	E.S.R. unchanged
7	M	58	18	80	+10%	+4	Nil on either	E.S.R. unchanged in the 40s
8	M	39	9	75	Unchanged	Unchanged	,,	,,
9	M	48	3	60	,,	,,	,,	E.S.R. normal on both
10	F	50	8	150	,,	,,	Nil	Compared with corticotrophin gel, 15 units daily
11	F	50	5	75	,,	,,	Nil on either	,,
12	M	47	8	50	,,	,,	Improved	,,
13	F	44	4	100	,,	,,	Unchanged	,,
14	F	50	3	25	,,	,,	Unchanged	Definite preference for dexamethasone. Best for years. E.S.R. normal in both
15	F	50	12	80	,,	,,	,,	,,
16	F	59	4	100	,,	,,	,,	E.S.R. on dexamethasone averaged 14; on prednisolone, 22
17	M	45	7	150	,,	,,	Nil on either	,,
18	F	44	2	70	,,	,,	Unchanged	,,
19	M	60	13	200	,,	,,	Nil on either	,,
20	F	54	18	16	−30%	−7	,,	E.S.R. normal on both
21	M	63	9	75	+60%	−6	Unchanged	Indigestion less with crushed tablets. E.S.R. normal with both
22	M	46	1	50	+30%	+9	Nil on either	E.S.R. normal with both
23	F	66	2	140	Unchanged	−2	,,	E.S.R. on prednisone 43. Average on dexamethasone 47
24	F	49	1	60	,,	Unchanged	,,	E.S.R. unchanged in 30s
25	M	45	8	110	,,	−4	,,	E.S.R. normal on both
26	M	70	8	120	,,	Unchanged	,,	,,
27	M	50	2 months	80	,,	,,	,,	E.S.R. just above normal; unchanged with both
28	F	47	4	100	,,	+3	Slight, unchanged with both	E.S.R. normal with both
29	F	34	6	150	Not done	Not done	Nil on either	,,
30	F	55	5	100	Unchanged	Unchanged	Unchanged	E.S.R. unchanged in the 50s; compared with triamcinalone 1 mg. dexamethasone=4 mg. triamcinalone

Grip was measured with sewn-up sphygmomanometer cuff, inflated to 30 mm. Hg. Erythrocyte-sedimentation rates (E.S.R.) (Westergren, uncorrected) 200 mm. tube read at one hour. Finger swelling was measured by jeweller's rings. 100% pain and stiffness means unchanged from symptoms on admission, below 100% indicates improvement, above deterioration.

The youngest, who had been on prednisolone for four and a half years, developed severe indigestion for the first time on transferring to dexamethasone.

Scleroderma

Of 2 women, aged 60 and 48, one was definitely better on dexamethasone with considerably less œdema, while the other was equally well controlled on either substance. In the former dyspeptic symptoms appeared on changing to dexamethasone.

Status Asthmaticus and Ankylosing Spondylitis

A man with status asthmaticus, aged 27, was equally well controlled by either substance.

A man, aged 52, with a sixteen-year history of ankylosing spondylitis, had been on prednisolone for sixteen months. On transferring to dexamethasone, he improved, becoming symptom-free, and, on returning to prednisolone he relapsed.

Discussion

When we received our first supplies of dexamethasone, the correct dosage in man had still to be ascertained. We therefore substituted tablet for tablet, 0·4 mg. dexamethasone (this being the strength of the first tablets received) for 5 mg. prednisolone. The disastrous results obtained in the first 2 cases showed us that this dose was totally inadequate, and we therefore doubled it. On this ratio the clinical results were very similar with the two substances. Shortly afterwards, when the strength of tablet issued was increased to 0·5 mg., we maintained the 1/2 tablet ratio; each patient, therefore, now received 1 mg. where previously he had had 5 mg. prednisolone. This 1/5 ratio is perhaps slightly in favour of dexamethasone; the true ratio may be more in the region of 1/6 or 1/7. This fact may explain the slightly increased incidence of gastric side-effects with dexamethasone. Nevertheless, from this small series of cases treated over short periods, there is little evidence that in the 5/1 dosage ratio dexamethasone was demonstrably superior to prednisolone except in a few cases.

The fact that much the same clinical effect is obtained with a smaller dose (1/5th) of the new substance is of little practical importance unless the cost is reduced in the same ratio, and this is not the case. The patient on dexamethasone has in fact to take almost twice as many tablets as with any other corticosteroid. It seems likely on the existing evidence that all the same side-effects occur with dexamethasone as with prednisolone and prednisone but on this series we can say only that the most frequent and annoying, i.e., gastroduodenal irritation, is no less common. We have not had patients with rheumatoid arthritis on dexamethasone long enough to know whether the negative calcium balance reported by Bunim et al. (1958) will prove an added disadvantage; when a daily dosage of 6 mg. dexamethasone was reached these workers found that around 1·05 g. of calcium was excreted daily, mostly in the fæces.

Summary and Conclusions

A new steroid, dexamethasone, has been compared with prednisolone in its effect on 30 patients with rheumatoid arthritis in a dose ratio of 1/5 over periods up to twenty-four weeks. Little difference was apparent, 12 patients preferring dexamethasone, 12 preferring prednisolone, and 6 being indifferent. Dyspeptic symptoms appear to be no less common with dexamethasone than with prednisolone.

In systemic lupus erythematosus (3 cases), scleroderma (2 cases), ulcerative colitis (1 case), and status asthmaticus (1 case), little or no difference was noted in therapeutic response. 1 patient with ankylosing spondylitis improved on dexamethasone.

Thus, in most cases, there is no obvious advantage in transferring to dexamethasone. Some patients, nevertheless, preferred it and did improve on it, and it is therefore useful to have yet another potent steroid available.

We are grateful to Messrs. Merck, Sharp & Dohme for supplies of dexamethasone (' Decadron ').

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THE DOSAGE OF DEXAMETHASONE AND TRIAMCINOLONE IN BRONCHIAL ASTHMA

E. STRESEMANN
M.D.
From the Asthma Clinic, Free University of Berlin

THE discovery of cortisone was quickly followed by the development of the more potent corticoids prednisone and prednisolone, and recently dexamethasone (9α-fluor-16α-methylprednisolone) and triamcinolone (9α-fluor-16α-hydroxyprednisolone). The latter two substances were made available at a time when their dosage was only tentative, and therefore it seemed appropriate to determine this as quickly as possible. Fortunately in our clinic we had a number of patients with chronic bronchial asthma, whose maintenance dose of prednisone had remained fairly constant for some time. These patients were changed to dexamethasone or triamcinolone, and the maintenance dose of these substances was estimated.

Method

Our patients had a history of asthma for many years, and had been under outpatient observation for a long time. In every case, routine treatment had been tried at first, and prednisone had been used only if it was evident that without it either dangerous attacks would occur, or permanent incapacity for work would result. The maintenance dose of prednisone was arrived at as follows: during the first 2–3 days of treatment the patient received 25 mg. daily; during the following 10 days the dose was reduced by 5 or 2·5 mg. per day every 2nd day until it had reached 12·5 mg. per day. In most cases this period brought about a considerable improvement, with decrease of dyspnœa and cough, and an increase in vital capacity. As a rule, however, some minor symptoms remained which required symptomatic treatment. From this point onwards the daily dose of prednisone was further reduced

every week by 2·5 or 1·25 mg. As soon as symptoms increased again, as confirmed by the amount of symptomatic treatment required, we assumed that the daily dose was lower than maintenance, and it was at once increased by 5–10 mg. per day to restore the previous state. After 4–7 days this was reduced again to an amount one step higher than that at which increasing symptoms had developed.

This method has been found to work well. It has the advantage that the maintenance dose as defined here is the smallest amount possible for continuous treatment, and thus will produce only a minimum of harmful corticoid effects. Moreover it allows of easy recognition of a relapse provoked by external factors, such as superinfection or exposure to allergens. In-patients are not included in our series, and the influence of entering hospital can therefore be excluded.

Our average maintenance dose of prednisone was 10·0 mg. per day, and varied from 7·5 to 12·5 mg. per day. When this level had been reached, prednisone was replaced by either 2 mg. of dexamethasone or 6 mg. of triamcinolone. If the asthma became worse, this dose was doubled and then slowly reduced until a maintenance dose was reached. If the asthma did not become worse, the dose was gradually reduced until the maintenance dose could be recognised.

To avoid misunderstandings it should be stated that by the expression maintenance dose is understood that amount of corticoid substance the decrease of which will lead to a definite deterioration within 3–6 days. Sometimes there are patients who appear to be maintained with 5 mg. of prednisone or even less. Such cases, which have also been described by Irwin and Burrage (1958) and Arnoldsson (1958), are usually patients with moderate or mild asthma, in whom corticoid treatment induces an improvement lasting for weeks or months. In these patients corticoids can often be gradually omitted without an immediate relapse; nevertheless deterioration usually occurs some weeks or months later, either spontaneously or after an upper respiratory infection, and necessitates resumption of corticoid therapy. Such patients are not included here as it is difficult to find out their true maintenance dosage.

Results and Discussion

Both dexamethasone and triamcinolone were found to be, weight for weight, more effective than prednisone, the former being about 5 times, the latter about 1·6 times more active. Some workers with triamcinolone have, in the meantime, estimated its efficacy as 1·2–2·5 times that of prednisone (Sherwood and Cooke 1957, Epstein and Sherwood 1958, Segal and Duvenci 1958). In our observations the individual variation in this ratio is rather small (1·4–1·9); in those of Sherwood and Cooke (1957) it is between 1·2 and 2·5. The variations with dexamethasone, however, are considerably greater, the ratio to prednisone varying from 3·0 to 8·0. With dexamethasone the maintenance dose in an individual patient cannot therefore be predicted with a similar probability as with triamcinolone.

NUMBER OF PATIENTS SHOWING SIDE-EFFECTS ON PREDNISONE, TRIAMCINOLONE, AND DEXAMETHASONE

Side-effect	Prednisone	Triamcinolone	Dexamethasone
Increase of appetite ..	4	1	6
Moon-face	3	2	6
Increase of weight ..	4	0	5
Œdema, severe	0	0	1
„ mild	0	0	2
Disturbance of sleep, or general restlessness ..	1	0	2
Dyspepsia	2	0	0
Total of patients treated	29	9	28

It is doubtful whether these two new substances offer any therapeutic advantages in comparison with the older steroids, for a lower dosage alone is no advantage, except for topical application. As to the side-effects (see table), our small number of observations does not permit definite conclusions, but the occurrence of œdema (which disappeared under prednisone) in 3 patients treated with dexamethasone is remarkable. There is also the possibility of a negative calcium balance caused by dexamethasone (Slater et al. 1959).

Summary

The effect of two new corticoids, dexamethasone and triamcinolone, was investigated in 29 patients suffering from chronic bronchial asthma and compared with that of prednisone. The mean ratio of the maintenance dose of prednisone to dexamethasone was 5·4/1, that of prednisone to triamcinolone 1·6/1.

I am indebted to Prof. H. Herxheimer for reading the manuscript, to Messrs. E. Merck (Darmstadt), Messrs. Stern (Hamburg), and Messrs. Lederle (Munich) for trial amounts of dexamethasone and triamcinolone.

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INTUBATION OF THE CARDIA FOR INOPERABLE CARCINOMA

ARNOLD GOUREVITCH
M.C., M.B. Birm., F.R.C.S.
SURGEON, UNITED BIRMINGHAM HOSPITALS

ANY interference with the mechanism of swallowing makes life difficult enough, but inability to swallow even saliva makes it intolerable. Advanced carcinoma of the lower end of the œsophagus or the fundus of the stomach may result in severe dysphagia or complete inability to swallow. Naturally if resection of the lesion offers any prospect of cure or even long-continued relief, then this is the treatment of choice. In some patients, however, the growth is so advanced or the clinical condition so poor that resection may be either technically impossible or too dangerous.

Gastrostomy in such cases has been universally condemned. After gastrostomy the patient can be fed but cannot swallow, and one has only to see these poor people continually spitting out frothy saliva to realise that gastrostomy has nothing to offer and that there is no acceptable alternative to swallowing.

A bypass operation such as an œsophagojejunostomy may be

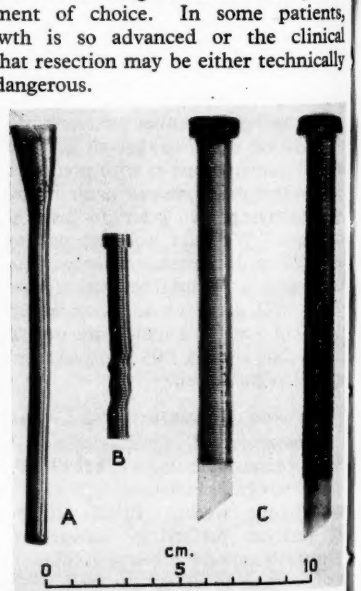

Fig. 1—A, Symonds' tube; B, Souttar's tube; C, flexometallic tube.

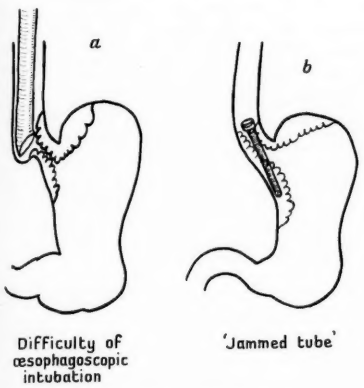

Fig. 2—Two possible difficulties in œsophageal intubation with Souttar's tube.

Fig. 3—Barium-swallow radiograph showing a Souttar's tube jammed in growth with a hold-up of barium and unrelieved obstruction.

Fig. 4—Model showing tube attached to bougie being drawn into position.

Fig. 4.

feasible. Even this, however, carries an appreciable mortality and may be difficult because of widespread cancer. There is in fact a simple method of restoring and maintaining the lumen until the patient succumbs to the disease.

In 1885 Sir Charters Symonds described "A case of malignant stricture of the œsophagus, illustrating the use of a new form of œsophageal catheter". Symonds' tube was a gum-elastic funnel (fig 1A), to which threads (rather like parachute cords) were attached so that it might be withdrawn and cleaned. This tube was passed blindly on a special introducer. The devising of this indwelling tube was an important development in the palliative treatment of œsophageal cancer.

In 1924 Souttar introduced his tube (fig. 1B)—a spiral of German silver wire, with a "twist" in it, to prevent its being vomited up. This tube, or some modification of it, is still widely used today and is probably the best device for maintaining the lumen in carcinoma of the œsophagus itself.

A wide range of other indwelling tubes has been devised. Nearly all these are introduced via an œsophagoscope.

At the cardia Souttar's tube, as usually described, may be ineffective for two reasons: (1) the angle between the œsophagus and the stomach at the cardia may be "frozen" by an advanced growth, and safe passage of a tube from above may be extremely difficult or even impossible (fig. 2a), a growth at the cardia may have arisen in the stomach, and in any case is of unknown extent. The introduction of a tube via an œsophagoscope is a blind procedure. Since it is introduced from above, there is no certainty that the lower end of the tube will clear the growth (fig. 2b). It is not unknown for a Souttar's tube introduced from above to "jam" in the growth so that swallowing remains impossible (fig. 3). Because of such difficulties I think that in a growth of the cardia, any method of introducing a tube should include opening the stomach at laparotomy. In this way the tube may be introduced with guidance from below, and the position of the lower end verified by direct vision.

My own method, which has been used in a few patients since 1955, does not require the passage of an œsophagoscope. It may be employed at the same time as exploratory laparotomy if this reveals a growth of the stomach, œsophagus, or cardia which is inoperable.

The Tube and Method of Introduction

The method employs two simple devices: (1) a modified flexometallic endotracheal tube of armoured latex about 16 cm. long (fig. 1C). (2) a gum-elastic œsophageal bougie with an "acorn" at each end.

The abdomen is opened, and the extent of the growth at the cardia is established. If it is considered to be

RESULTS OF INTUBATION IN 6 PATIENTS

Case no.	Age (yr.)	Lesion	Indication	Operation	Result	Interval (weeks) between operation and death
1	62	Carcinoma of cardia	Dysphagia	Intubation	Swallowed well till death	18
2	59	Recurrent carcinoma after total gastrectomy	,,	Intubation	Fistula formation	5
3	78	Carcinoma of cardia	,,	Intubation	Swallowed well till death	20
4	80	Carcinoma of cardia	,,	Intubation	Swallowed well till death	18
5	76	Linitis plastica	,,	Intubation+gastroenterostomy	Fulminating bronchopneumonia, death	..
6	49	1. Recurrent carcinoma after gastrectomy 2. Further recurrence	,,	1. Intubation 2. Intubation+gastroenterostomy, 4 mos. later	Swallowed well after each operation	30

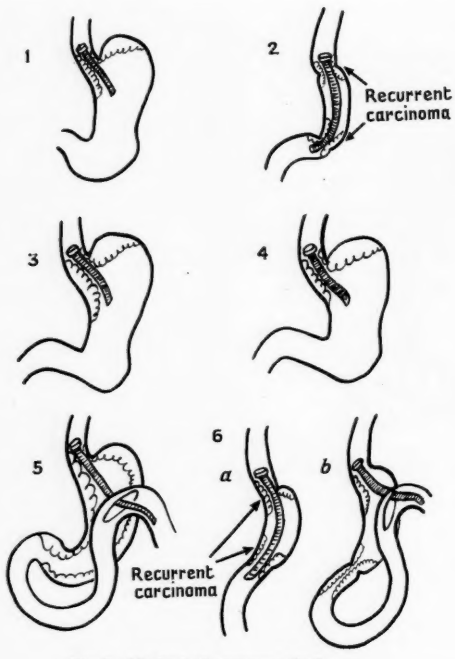

Fig. 5—Method of treatment in 6 cases.

inoperable, and the patient unsuitable for palliative resection or bypass, intubation is carried out as follows:

The stomach is opened. The fingers or the whole hand are introduced, and the orifice of the cardia is located. The anæsthetist passes the bougie blindly down the œsophagus. By manipulation the bougie is passed through the cardia into the stomach. The tube is tied securely on to the proximal end of the bougie. The tube is then pulled down into place (fig. 4) until the flange rests on the upper limit of the growth. The bougie is then detached. The distal end of the tube is seen to be clear of the growth and the incision in the stomach is closed. Alternatively if difficult to pass from above, the bougie may be passed up from the stomach by the surgeon, grasped by the anæsthetist, and pulled out of the mouth. The anæsthetist then attaches the tube, which is pulled down into position as already described, and the stomach is closed.

The stomach wall may be infiltrated by growth, and in one of my patients (case 2) a fistula occurred through the gastric incision. If the stomach cannot be safely closed, then an anterior gastroenterostomy should be carried out, using the incision into the stomach.

It is, I believe, a feature of the stomach wall, that even if infiltrated by carcinoma, it will usually take stitches, and heal satisfactorily.

I have recently had the advantage of seeing an œsophageal catheter designed by Dr. Mousseau and Dr. Barbin, and made by Porges of Paris. As a result I have modified the flanged tube so that the distal end tapers. It is then a tighter and better fit on the bougie. When the tube is in position in the stomach, the tapering end is cut off. I have not yet used this modification in a patient, but in practice it would probably be better than the non-tapering tube.

Results

The accompanying table sets out the results of intubation in 6 patients and fig. 5 illustrates the procedure in each case. In cases 1, 3, and 4 the growth was confined to the upper portion of the stomach, cardia, and lower œsophagus. After intubation these patients survived for an average four months, and they went on swallowing solids and fluids until they died.

In case 5, linitis plastica was present. An anterior gastroenterostomy was done and the tube passed through the stoma. This patient, who was 76 years old, developed a fulminating bronchopneumonia and died the day after operation.

In case 2 total gastrectomy for carcinoma had been done with a jejunal loop interposed between œsophagus and duodenum, four months previously. The patient returned with a recurrence at both suture lines. A tube was put down through both areas of growth, but when the jejunum was sutured it was under tension. A fistula resulted, and everything the patient swallowed came out through the abdominal wound. This decided me in future to do an anterior gastroenterostomy if there was any likelihood of fistula formation.

Case 6 had had a near-total gastrectomy eighteen months previously, and carcinoma had recurred in the gastric remnant. A tube put through enabled the patient to swallow for four months. A further recurrence developed in the duodenum, and an anterior gastroenterostomy was done, the tube being passed through the stoma. The patient was able to swallow in comfort till she died about three months later.

I believe this device has a place in the management of inoperable carcinoma of the cardia, or in recurrence following radical surgery.

Summary

A flexible metal tube is described which, inserted at laparotomy under direct vision, enables patients with inoperable carcinoma of the cardia to swallow during their last weeks or months of life.

I should like to express my indebtedness to my colleagues, Mr. Victor Brookes and Mr. Denis Morrissey, for allowing me to cite cases 4 and 6 respectively.

The tubes have been made for me by Messrs. T. H. Spicer and Son, 29, Willoughby Road, London, N.8, and the gum-elastic bougies by Messrs. Down Brothers, Mayer & Phelps Ltd., Church Road, Mitcham, Surrey.

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THE COUNTRYMAN'S PROSTATE

J. K. WILLSON-PEPPER
M.A., M.B. Cantab., F.R.C.S.
SURGEON, THE YORK GROUP OF HOSPITALS

PROSTATIC disorders occur wherever civilised man achieves the biblical threescore years and ten, and the more he is rustic of mind and rural of domicile the longer he waits before recourse to medical assistance. Even then the battle is not fully engaged; for where hospitals are concerned distance does not lend enchantment, and he may well resist to the last all attempts at persuasion and demand the blessed relief of catheterisation in the home, to be repeated on numerous occasions before he and his family can be brought to accept what they fear may be his last journey.

At last he arrives, grief-stricken and full of dread, in the hard-driven surgical ward of his local hospital—one sufferer in an ever-flowing tide of human affliction. If the hospital is small, he may be received in the one and only male surgical ward, to which all accident cases, surgical emergencies, and orthopædic and general surgical cases are sent—a ward with every bed along the walls occupied and beds ranged down the centre; blood-transfusions, intravenous saline drips, gastric suctions, bladder drainage, and the like in progress on all sides; the ward sister and nursing staff pressed to the limit of their physical powers; the house-surgeon in the theatre involved in an operating-

list with his chief; and the surgical registrar, if this appointment has been filled, deeply engaged with some other case. This then may be the background before which the bad-risk prostatic case takes the stage; and if we are not to have Hospitals "B", as well as "A",[2] with uræmic old men climbing up the wall, we are going to have to stick to a few simple and sound basic principles.

Our two biggest problems may present at the very outset—uræmia and sepsis.

My purpose is not to offer opinions on the many controversial topics which arise in all such cases wherever they may be treated, but to focus only on the special difficulties in the smaller centre, which is hard-driven and which has in its care a proportion of chronically ill and aged patients. If we are to achieve a safe return to his home of the octogenarian, on his feet, in a short time, in good heart, and with restored powers of micturition, great vigilance and a lively anticipation of trouble will be needed.

Management

General Measures

What is good for an octogenarian is probably no bad thing for a man ten years younger: many of these old patients are suffering from lack of sleep and some from subclinical heart-failure. The relief of continuous bladder drainage may transform their physical and mental state in the course of days or of a week or so. Delay means occupying bed space, extra nursing care, little escorted walks up the ward, breathing exercises, biochemical investigations, and chemotherapy. But, pressing as may be the need to clear the ward of all except immediate preoperative and postoperative cases, it is yet of prime importance that these old men should get used to the sisters, nurses, and doctors who are going to help them through the great crisis of their lives—the operation.

Where complete retention has not occurred and where the urine has not been infected, unless there is evidence of gross biochemical imbalance, I have avoided catheterisation, in the hope that, after a full assessment, definitive surgery may be undertaken as a primary procedure. Even if routine immediate prostatectomy for acute retention had stood the test of time, there are many hospitals in this country where it would have been a practical impossibility, because there would not have been adequate laboratory, surgical, and nursing staff, not to mention theatre accommodation. In the case of complete retention, steps must be taken to drain the bladder by some means or other forthwith.

Preoperative Drainage

But the price paid for this invaluable respite on bladder drainage will be too high if the uninfected cases become infected, and if the patient with a drug-sensitive *coli* in pure culture acquires from his neighbour or from the hands of the attendant a *proteus* or *pyocyanea* infection which may defeat outright the entire *British Pharmacopœia*. To prevent this in a hard-pressed ward a few basic rules may help.

To break the chain of cross-infection at every possible link all indwelling catheters are ruthlessly discarded after they have been used on one patient. All syringes used for irrigation are of the piston pattern (Riches or Wardill) because unless especial care is taken to fill with water the rubber bulb of a syringe of the Canny Ryall type before boiling, the heavily contaminated interior of the bulb will remain unsterilised, a point not always remembered. All containers for urine are autoclaved in batches, brought to the ward ready for use, and changed daily. Only closed drainage systems are employed.

Liquid formaldehyde provides a sterilising vapour,[4] and is put into all urine containers. Inexperienced nurses sometimes put in some other antiseptic, not realising that sterilisation of the tubing by vapour is the main purpose of the formaldehyde. All tubes and connections are sterilised in the autoclave, and made up in appropriate lengths in a marked drum, each in its separate packet. Sterilised gloves are used for dressings.

Whenever possible I use an indwelling Gibbon [5] polyethylene catheter for preoperative drainage, which I regard as one of the blessings of humanity. One of these will frequently pass when a Foley catheter will not, and the risk of urethritis is negligible. It will not, of course, transmit solid debris or allow of irrigation; and it is therefore not suitable for the immediate postoperative period.

Urethral drainage provides breathing-space which allows full assessment of the case; but, when it fails, a number of alternatives loom up. The choice then lies between semirigid catheters of the 'Neoplex' type, some form of suprapubic drainage, or a perineal urethrostomy. Before the advent of the Gibbon catheter, in many cases we employed Riches' suprapubic stab technique.[3] This is quick, usually easy, and, with proper care, safe. But if suprapubic drainage of any sort is continued for long, sepsis round the skin opening—and before long in the bladder—is apt to become a nasty hazard. I should like, therefore, to make a plea for perineal urethrostomy in some old patients who will, in due time, be fit for prostatectomy, but whose general condition is as yet far from satisfactory, and in whom for one reason or another the anterior urethra cannot be used to transmit a suitable indwelling catheter The tendency of some patients to pull out their catheter, even with the bag inflated, and preferably at the most inconvenient times, seems to be absent when the perineal route is employed, presumably because this approach causes so little discomfort. Furthermore it drains the bladder from the bottom and leaves the suprapubic skin and the approaches to the bladder untouched.

Hæmorrhage

Hæmorrhage and clot retention are never exactly welcome; but in the aged they rapidly become a menace, More insidiously, prolonged postoperative bleeding which quietly exsanguinates will increase the risks of coronary and cerebral thrombosis and of pulmonary embolism—an even greater danger to the aged, in my opinion. In such circumstances special precautions are advisable.

The margin of safety is greatly widened by blood-transfusion, and I am convinced that delayed catastrophe can often be prevented by a continuous slow transfusion covering the few hours immediately following operation. Patients receiving this timely replenishment often look and feel fitter on the day after their prostatectomy than at any time before it. If incipient cardiac failure and chronic chest conditions have had preoperative inpatient treatment, the risk of overloading the tired heart will be small; and the knowledge that the patient is in credit with blood enables the anxious surgeon to stay his hand a little longer when he sees an alarming seepage of blood passing out with the urine at a time when hæmaturia should be subsiding.

Clot Retention

The old man with clot retention is a special problem in the smaller general hospitals, where staff shortage is common. Attempts to prevent it may occupy one nurse almost exclusively for several hours. In the interest of strict asepsis, syringing and other forms of irrigation have come in for a measure of criticism; and it would be wonderful to feel that they were never really necessary. Unfortunately they are.

In a really hæmorrhagic case, continuous through

irrigation with a " third ureter " as suggested by Wilfrid Adams [1] will earn the ward staff's heartfelt gratitude and often save a return visit to the theatre. If a self-retaining suprapubic catheter is used for this purpose, its withdrawal is liable to tear open the wound track, unless it is of the Foley pattern: with this type the tissues tend to fall together and suprapubic leakage may be little or none.

Discussion

Prostatic cases make heavy demands on all concerned. The strain can be minimised by a simple routine; but, when planning such a routine, it is desirable that it should be sound in theory and simple in execution. It is not yet universally accepted that infection of the urinary tract from catheters, apparatus, and attendants is both frequent and, with some techniques, inevitable. Discarding catheters after each case may seem an unwarrantable extravagance, but the cost of staying in hospital because of cross-infection can soon become far greater.

The rinsed-out Winchester bottle under the bed, with the end of a rubber tube hanging loosely in its neck, and with its comforting quota of clean-smelling disinfectant in the bottom, is still in use, though no amount of disinfectant or detergent rinsing will rid it of organisms deposited by a long succession of urinary cases.

By organising an exchange of freshly autoclaved urine containers, delivered daily to the ward to replace the used ones, the ward staff is relieved of time-consuming ward sterilisation. An efficient autoclave technique will also guarantee the destruction of all organisms that might pass from one patient to another by this route. Similarly, by making up in advance separate packets of tubing and connections to be autoclaved in a marked drum, each is immediately available, and all serious risk of contamination is eliminated.

Routine blood-transfusion on all open prostatectomy cases may sometimes be unnecessary, but it can seldom be wrong; and it is a safeguard against delayed disaster.

Summary

The management of the prostatic case in hospital is often anxious and makes big demands on the ward staff. Suggestions are made whereby the care of such cases may be simplified to relieve the strain in smaller surgical centres.

I wish to express my grateful thanks to the doctors and nurses who have worked with me, and in particular to Sister Vivienne Patterson and Sister Sheila Lish, whose vigilant care and practical suggestions have contributed much to the recovery and well-being of the patients in their charge.

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" . . . I feel sure that we ought to resist too much paring down of our responsibilities for advancing knowledge within the framework of university courses. . . . It is, of course, arguable that no line of research lives for ever and that it may be better for a research team to have the immediate advantages of freedom from university duties in spite of the long range disadvantages. Many of these can be avoided if there is good will on both sides, but it is easy for ill will to arise when the two sides work under such different conditions, when the full-time research man at an institute can envy the amenities of a university and a busy university lecturer can find no time to get on with his research." —Lord ADRIAN, in an address to the Rockefeller Institute, New York, on May 21.

PROSTATECTOMY FOR RETENTION OF URINE

W. B. N. BOMFORD
M.B. Lond., F.R.C.S.
LATELY SENIOR SURGICAL REGISTRAR, KING GEORGE HOSPITAL, ILFORD

PROSTATECTOMY is a common operation, but the question of when and how it should be performed is still debated. Though its results are often gratifying to the surgeon and beneficial to the patient, they can also be disheartening to the one and disastrous to the other.

The Lancet (1956) suggested that all hospitals should aim at the high standards set by special units; but comparison of results must take into account the varying proportion of patients whose outlook is made worse by preliminary catheter drainage (Hickinbothan 1956).

Material and Management

During my two years as resident surgical officer at King George Hospital, Ilford, some 70 patients were admitted to the surgical wards with retention of urine; and 55 of these had true retention due to prostatic enlargement. In fewer than 10 was prostatectomy performed for symptoms which fell short of actual retention.

Nearly all cases of retention were treated in the same way: after initial catheter drainage or decompression, a short period of investigation and assessment was followed by operation. 45 cases were diagnosed as acute retention on admission, and relieved by immediate emptying by catheter: 10 who showed evidence of chronic retention were treated initially by slow decompression.

The operative techniques included those described by Freyer, Harris, Wilson Hey, and Millin. Most patients returned to the ward with a suprapubic tube and had continuous bladder irrigation or suction for forty-eight hours. The postoperative management of the catheter was by no means rigid, each case being considered separately; but in general the suprapubic tube was removed as soon as the urine was free from blood and pus on naked-eye examination. The urethral catheter was withdrawn when the suprapubic wound had been dry for three days at least; but in many cases it was retained for longer periods, up to seven days.

The average age of the 55 patients was 70 years, the oldest being 88 and the youngest 53. They spent an average of thirty-seven and a half days in hospital, but in some cases this period included more than one admission. 43 (78%) were subsequently fit for prostatectomy in one or more stages. The number of deaths in the whole series was 7 (13%), and 4 of these 7 patients had had a prostatectomy.

Discussion

Lee et al. (1957) compared the results of prostatectomy in teaching and non-teaching hospitals: they reported that of 660 teaching-hospital patients 41 (6%) died, whereas in non-teaching hospitals 48 died out of 280 (17%). The difference in the total numbers may reflect the difficulties in tracing case-notes in smaller hospitals which do not keep an index of diseases: the difference in mortality, I would suggest, may well be due in part to retention of urine in most patients admitted to non-teaching hospitals.

Wilson Hey (1945) divided his prostatectomy material into four groups. His group I included 189 " perfect cases " whose mortality was 2%. Group II consisted of 174 patients with mild systemic disease, and a mortality of 7%. In group III were 31 patients with " marked systemic disease " and a mortality of 16%. 6 patients in renal or cardiac failure comprised group IV; and 4 of those (66%) died.

MacEachern (1958) reported 131 cases of acute retention with a mortality of 6%, and 222 cases of prostatectomy with a mortality of nearly 5%. The average age of his patients was 67, and the average length of their stay in hospital was twenty-seven days.

Scorer (1953) called routine immediate prostatectomy "a counsel of perfection"; and he pointed out that it demanded a team or unit that was often not available. Of his 150 cases of retention treated by suprapubic catheter 87 (58%) came to prostatectomy. Some of the remaining patients were relieved spontaneously, others proved to have a stricture or suffered a permanent suprapubic catheter; but 23 died without further treatment, 16 from causes unrelated to the prostatic condition.

The series reviewed here is small; but it gives a picture of the results with unselected patients treated in a general surgical ward. Each of the 4 cases in which death followed prostatectomy illustrates one of the difficulties peculiar to this operation.

Case 1.—This was a man of 82 whose blood-urea was 40 mg. per 100 ml. and whose hæmoglobin of 48% was raised to 84% by blood transfusion. His prostate proved to be carcinomatous, and did not shell out when approached by the retropubic route. About three-quarters of it could be dissected out; but the patient died on the fourth postoperative day. A suprapubic tube and œstrogens would have given him a better chance than an attempt at partial removal; but it is not easy to know when to stop. Often a fibrous gland can be winkled out with care. "What happens in the hidden depths determines in the highest degree the safety or otherwise of the operation" (MacEachern 1958).

Case 2.—The general health of this 65-year-old man was good. Because of severe bleeding during his retropubic operation a pack was left in the retropubic space. Removal of this pack started off a secondary hæmorrhage; and this precipitated auricular fibrillation. He died three weeks after operation. His loss again showed the importance of carefully securing the large veins which run over the capsule of the prostate. Failure to do so—and the need for a pack to control the bleeding—endangers the success of the whole operation.

Case 3.—This patient was a fit old man of 84 who had been catheterised on a day trip to Ramsgate. He refused admission there, and his retention recurred. He was a little disorientated on admission here; and remained disorientated after his retropubic prostatectomy. He died four weeks later. His case illustrated that all patients who require catheterisation for acute retention should be admitted to hospital, and it underlines the hazards of non-cooperation from the postoperative patient.

Case 4.—This man of 82 died from a secondary hæmorrhage a week after operation, having already developed postoperative congestive heart-failure. Though emphysematous, he had been otherwise well before operation; but the elderly patients have little reserve for withstanding secondary bleeding.

Summary

Most patients admitted to general surgical wards for prostatectomy have retention of urine; and some are very poor risks.

The lessons learned from 4 deaths are described.

I am very grateful to Mr. Harold Dodd and Mr. G. C. Tresidder for help given in writing this article, and I am indebted to the staff of King George Hospital, Ilford, whose patients were studied.

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ELECTROCARDIOGRAPHIC FINDINGS IN ACUTE INTERSTITIAL MYOCARDITIS

JEHOSHUA HEICHMANN
M.D. Lwow

HARRY BASSAN
M.D. Sofia

From Medical Department A, Rambam Government Hospital, Haifa, Israel

ACUTE interstitial myocarditis was first described by Fiedler in 1899, and since then many papers have discussed the ætiology, and the clinical and epidemiological aspects of this disease. The electrocardiographic (E.C.G.) findings have been described by various authors, but most of them based their observations on a small number of cases (Faber and Fischer 1956, Keller 1945, Lind and Hulgest 1949, Madsen 1951, Rosenbaum et al. 1953). We have been able to study E.C.G.s in 21 children with acute interstitial myocarditis.

Clinical and Pathological Findings

Between March, 1956, and October, 1957, 57 children with acute interstitial myocarditis, all from the Haifa area, were admitted to our hospital (Falk and Elkon, Freundlich et al. 1958). All were aged between six months and three and a half years, and most of them were well nourished. The onset of the disease was sudden, and often followed a mild upper respiratory infection.

The physical signs were those of acute heart-failure. The children were restless and dyspnœic, with striking pallor of the face and cyanosis of the lips; the extremities were cold and livid. The pulse-rate was between 140 and 200 and the heart-sounds were faint and no murmurs were present. Moist rales were heard in the chest, and the liver was much enlarged. Chest X-ray invariably showed enlargement of the heart shadow, which was usually very big (Munck and Lederer 1958). Occasionally the individual cardiac segments could no longer be differentiated, and the X-ray appearance resembled that of pericardial effusion.

Despite intensive treatment for heart-failure, antibiotics, and steroid therapy 50 children (87·7%) died, usually within twenty-four hours of the onset of heart-failure. Necropsy in 49 showed uniform dilatation of the heart, which weighed 70–100 g. (normal for this age, 30–70 g.). In several cases there was a clear yellow pericardial effusion (50–100 ml.). There were no valvular lesions and no congenital heart defects, but in slightly under half the children there was a whitish thickening of the endocardium in the subaortic region, which on occasion resembled fibroelastosis. The lungs were œdematous and congested, and in half the cases bilateral hydrothorax of 100–250 ml. was present. The remaining organs were acutely congested.

The histological appearances of the myocardium were those of severe interstitial infiltration with small, round, lymphocyte-like cells. These were usually arranged diffusely but sometimes were grouped in patches: they bore no relation to blood-vessels, but tended to be more pronounced towards the epicardial surface. Patchy degeneration of the myocardium was often seen. The thickening of the myocardium was due to the infiltration, and not to true hypertrophy of muscle-fibres. In nearly half the cases there was moderate, round-cell infiltration of the epicardium, and in more than half some thickening of the endocardium by a moderate proliferation of both elastic and collagen fibres, and occasionally by some round-cell infiltration.

All attempts, including animal inoculation from postmortem material, failed to isolate a bacterial or viral agent.

Electrocardiographic Changes

Because of the serious condition of the children on admission we recorded E.C.G.s in 21 cases only; all the

other patients died before this examination could be made. Of the 21 patients who had an E.C.G. 14 died, and 7 recovered. (E.C.G.s had been taken in 2 children before the onset of the illness, and these had shown a physiological record, with a normal QRS axis.) The E.C.G. changes were similar in every case.

All the children had sinus tachycardia (between 140 and 200 per minute). P waves were normal in 6 cases, tall (more than 2 mm.) and peaked in 8, and peaked only in 7. The QRS complex showed low voltage (5 mm. or less in the unipolar limb leads) in 12 cases. In 4 the electrical axis of QRS was normal (between 20° and 90°); in the remainder there was considerable right-axis deviation. The PQ interval was always normal (0·10–0·16 sec.). QRS did not exceed 0·07 sec. The ST segment was below the isoelectric line in 5 cases, slightly above in 5, and much above in 2. In all 21 children the T waves were flat. In 1 T was inverted in the precordial leads, and flat in the other leads; in 2 T was upright in V_1 and V_2, and flat in the other leads (the T waves became normal and inverted in V_1 and V_2 after recovery). In 1 case the record indicated a wandering pacemaker.

The E.C.G. became normal within four to six weeks of recovery in all the 7 patients who survived. (E.C.G.s had been taken in 2 children before the onset of the illness, and these had shown a physiological record, with a normal QRS axis.)

These E.C.G. findings correspond to the clinical and pathological features, but are not specific. Despite severe injury to the heart muscle, sinus rhythm was maintained, and there was no evidence of conduction defect. In other instances of myocardial damage (e.g., diphtheria, rheumatic fever, and poliomyelitis) there is almost always some damage to the conducting mechanism. This supposition, based on E.C.G. findings, that the conducting tissue was undamaged was confirmed by histological examination. Our pathologist (Dr. B. Geli) examined sections of the heart from 10 cases and found no evidence of pathological change in the conducting tissue, although the rest of the heart-muscle showed gross abnormalities.

The absence of such damage may, therefore, be a diagnostic sign of acute interstitial myocarditis, and it is possible that the unknown causal agent does not attack conducting tissue, or that this system is immune to the agent.

Summary

Between March, 1956, and October, 1957, 57 young children with acute interstitial myocarditis were admitted to Rambam Hospital, Haifa, and 50 died. We recorded an electrocardiographic tracing in 21 cases: the main features were sinus tachycardia, low voltage complexes, frequent high and peaked P waves, right-axis deviation, and alterations in the ST segment and T waves.

Despite severe myocardial damage, a defect in the conduction mechanism was never seen. This finding may be a diagnostic feature of acute interstitial myocarditis.

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HÆMOPHILIA A IN A "GIRL" WITH MALE SEX-CHROMATIN PATTERN

INGA MARIE NILSSON
M.D. Lund
OF THE DEPARTMENT OF MEDICINE, UNIVERSITY OF LUND, AND ALLMÄNNA SJUKHUSET, MALMÖ, SWEDEN

S. BERGMAN
M.D. Lund
OF THE BACTERIOLOGICAL INSTITUTE, UNIVERSITY OF LUND

J. REITALU
Ph.cand. Lund
OF THE CANCER CHROMOSOME LABORATORY, INSTITUTE OF GENETICS, UNIVERSITY OF LUND

J. WALDENSTRÖM
M.D. Lund
PROFESSOR OF MEDICINE, UNIVERSITY OF LUND; PHYSICIAN TO ALLMÄNNA SJUKHUSET, MALMÖ

CLASSICAL hæmophilia (antihæmophilic globulin deficiency) is transmitted by a sex-linked recessive gene and is therefore very rare in females. The homozygous hæmophilic state in the female can result from the marriage of a hæmophilic man to a woman who is a carrier of the disease. Four such cases of true hæmophilia in the female have been reported (Merskey 1951, Israëls, Leinpert, and Gilbertson 1951, Pola and Svojitka 1957). Also Brinkhous and Graham (1950) have shown the occurrence of hæmophilia in the homozygous female dog.

Quick and Hussey (1958) have reported the case of an 11-year-old girl with a coagulation defect indistinguishable from classical hæmophilia A, except that the family history was negative. A case of hæmophilia A has also been described by Choremis et al. (1956) in a 2-year-old girl with unknown family history. These seeming exceptions to strict sex linkage in hæmophilia have not been explained, and Quick and Hussey suggested that their patient's condition was caused by mutation.

We report here a case of severe hæmophilia A in a girl, in which chromosome studies have explained the apparent exception from sex-linked inheritance. The child, who had female external genital characteristics, was shown to have a male sex-chromatin pattern.

The Case

The patient, a child aged 16 months, had always bruised readily. At 12 months a trivial trauma of the thigh gave rise to a large hæmatoma, for which she was admitted to hospital. A prolonged coagulation-time was then observed. On a later occasion a large hæmatoma followed lumbar puncture. The hæmoglobin fell from 11·2 g. per 100 ml. to 4·6 g.; and she received repeated blood-transfusions. She had had long episodes of nose-bleeding. There had been no bleeding into joints, but the child had not yet learnt to walk.

Family History

Fig. 1 shows the pedigree. One of the patient's brothers had died soon after birth, with bleeding. There was no consanguinity between the parents. None of the paternal ancestors had any known bleeding tendency and the father's coagulation-time, bleeding-time, and plasma anti-hæmophilic globulin (A.H.G.) were normal. The patient's mother (IV: 4) belonged to a hæmophilic family (Sköld 1944, fam. 22). Two (IV: 6 and V: 13) of the hæmophiliacs in that family had been investigated by us and had been found to have severe hæmophilia A with A.H.G. activities of 0·1% and 0·2%. The patient's mother (IV : 4), and her maternal cousin (IV : 11) with a hæmophilic boy, had A.H.G. activities of 25% and 35%. The only coagulation defect found in the carriers and bleeders in that family was a low A.H.G. value.

None of the maternal or paternal ancestors had had any

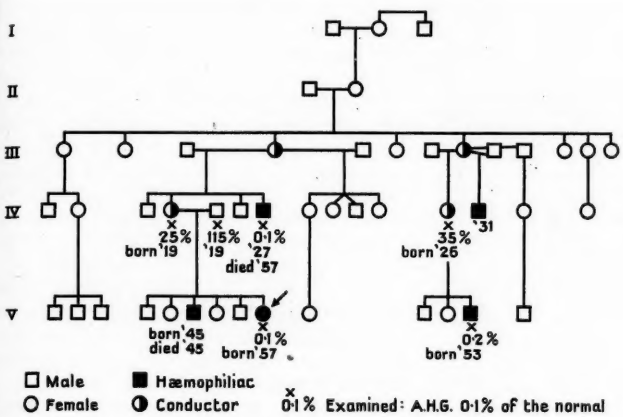

Fig. 1—The pedigree.

other known congenital malformations. The mother's blood was group A Rh-negative and the father's group A Rh-positive.

Examination and Investigations

The girl was of normal size for her age (fig. 2). She had several hæmatomas but no petechiæ. No congenital malformations such as digital anomalies or webbed neck were observed. Physical and radiological examination did not reveal any signs of congenital heart-disease. The external genital characteristics were of female appearance though the labia minora were small and the clitoris somewhat large for the child's age; no uterus could be palpated per rectum, and the hymen appeared to be imperforate (Prof. S. Genell).

The patient belonged to blood-group A Rh-positive.

Coagulation studies were performed by previously reported method (Nilsson et al. 1957) and gave the following results: coagulation-time 120 min. (normal value 4-8 min.); bleeding-time 4-5 min.; platelet count 320,000 per c.mm.; prothrombin consumption 118%; fibrinogen 0·34 g. per 100 ml. The one-stage prothrombin-time was normal; the prothrombin and proconvertin (Owren's P & P) value was 112%, the factor V value was 120%. The plasma A.H.G. activity, as determined by the recalcification method on hæmophilia-A plasma, was 0·1%. The hæmophilia-B-factor content of the plasma was 60%. The prolonged recalcification-time of the patient's plasma was corrected by the addition of normal plasma, $BaSO_4$-adsorbed plasma, hæmophilia-B plasma, and human fraction I-O containing A.H.G. (Blombäck and Nilsson 1958). On the other hand, addition of hæmophilia-A plasma had no effect. No anticoagulants could be detected to explain the delayed coagulation. There was no fibrinolysis.

Thus the laboratory findings in this patient were identical with those obtainable in severe hæmophilia A in males.

Genetic Studies

Sex determination on blood-films was performed by the method of Kosenow (1956). Among 500 neutrophil polymorphs 1 leucocyte with an appendage of type A or drumstick was found, 3 with the appendages of type B, and 68 with appendages of type C. This result was thought to indicate a male chromosomal pattern.

Studies of resting cells from skin specimens by the method of Reitalu (1957) also indicated a male sex pattern.

Skin biopsy was performed twice for culture and cytological study. Because of the bleeding tendency attempts were made to remove the specimens from the epidermis only (left elbow fold and right thigh).

The bits of skin were cultured by the method of Reitalu and Bergman (1959). The medium was changed every third day. Epithelium-like cells gradually grew out, and after 3 months the yield in two Carrel flasks was sufficient for investigation. The contents of the two Carrel flasks were transferred to slides (Bergman 1959).

The mitotic frequency was low. A few of the cells divided on the fourth day after transfer to the slides. These cells were exposed to colchicine, fixed, and stained in the manner described by Bergman et al. (1959). In fig. 3 the chromosomes from a cell are shown after arrangement in pairs. The cells in the metaphase had 46 chromosomes, 5 of which were small and acrocentric. Of these, 3 were similar and 1 of them was presumed to be the Y chromosome. It was not possible, however, to exclude the possibility that 1 of the 2 small autosomal pairs was trisomic (fig. 3). One of the large subterminal chromosomes had no partner and ranked in size between the 5th and 6th pairs. The quotient between the length of the long arm and the short arm of this chromosome was 1·90—i.e., close to that given by Tjio and Puck (1958) and by Chu and Giles (1959) for the X chromosome.

Discussion

Three possibilities were considered: (1) the child might be a homozygous hæmophilic female by inheritance or mutation; (2) the child might be a heterozygous female (carrier) with unusual bleeding tendency; or, (3) the child might have a male chromosomal pattern.

Heterozygous inheritance of the hæmophilic gene was possible, since the mother was a true carrier of hæmophilia A; but homozygous inheritance was unlikely since the father was not affected and nothing suggested that the child was not his offspring. Moderately decreased A.H.G. values have been found in females who are heterozygous for the hæmophilic gene (Nilsson et al. 1959), but as a rule these females do not bleed more readily than normal. There are only a few reports of heterozygous females with increased bleeding (Fantl and Margolis 1955, Douglas and Cook 1957, Taylor and Biggs 1957, McGovern and Steinberg 1958). These females belong to families with mild hæmophilia A and had symptoms similar to those seen in males with mild hæmophilia. Our patient, however, had symptoms of severe hæmophilia A with an A.H.G. activity of only 0·1%. The results of the coagulation investigation of the patient were also the same as those found for the hæmophilic male relatives in her family. The female carriers in the family, on the other hand, had A.H.G. values of 25% and 35% and no bleeding symptoms. To explain the coagulation disorder of this child by the assumption that she was a female carrier of hæmophilia with unusually low A.H.G., therefore appeared unsatisfactory.

Fig. 2—The patient.

The occurrence of hæmophilia in this girl, who might be heterozygous for the hæmophilic gene, could be due to

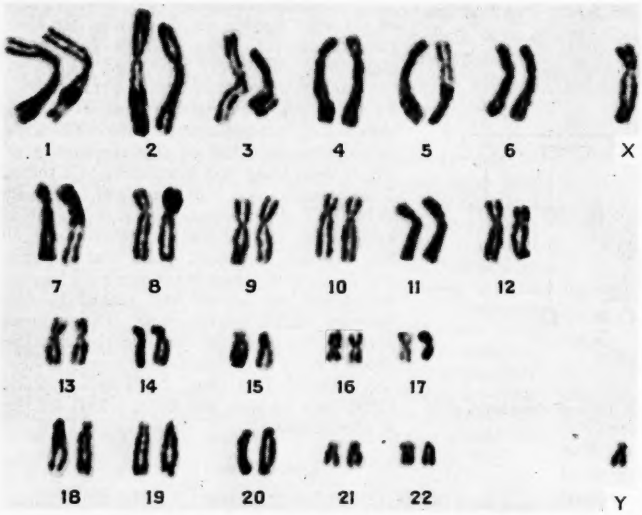

Fig. 3—The chromosomes of a cell arranged in pairs.

a mutation of the other X chromosome, resulting in a homozygous female. This possibility was eliminated by chromosome studies which showed that the patient did not have a XX chromosomal constitution (fig. 3).

The chromosome studies showing a male sex-chromatin pattern offered the explanation. Hæmatological sex determination by the method of Kosenow (1956) indicated that the nuclear sex was male. Tissue culture of skin specimens and cytological studies showed 46 chromosomes and a probable XY sex chromosomal constitution (fig. 3).

Our knowledge of the morphology of the sex chromosomes is as yet not sufficient to permit identification with certainty. Even their position in regard to size among the autosomes is uncertain and shows variation. According to Tjio and Puck (1958) the Y chromosome lies between the 20th and 21st pair according to size and is one of the largest among the 5 small acrocentric chromosomes. Chu and Giles (1959) place the Y chromosome after the 22nd pair, which implies that it is the smallest. The X chromosome according to Tjio and Puck should be placed between the 4th and 5th, according to Chu and Giles the 5th and 6th pairs, and according to Ford et al. (1959a) it is believed to be the 7th in order of length.

In our patient two possible genetic constitutions must be considered—XY or XO. According to the first alternative the patient is a chromosomal male. According to the second the patient could be a female with an abnormal genotype as described by Ford et al. (1959b) in a chromatin-negative case of Turner's syndrome in which the bone-marrow cells proved to contain 45 chromosomes and in which the sex chromosomal constitution was determined as XO. But our patient had no congenital malformations such as digital anomalies, webbed neck, or evidence of heart-disease which are common in Turner's syndrome. The child's age made an exact sex determination impossible and the possibility that she is a hermaphrodite cannot be determined until she has reached sexual maturity.

It appears probable that the sex chromosomal constitution of the patient was XY. Such an interpretation also agrees with the results of the hæmatological sex determination and the studies of resting cells.

We may ask ourselves whether similar observations might have been published without complete clarification. It is possible that the two instances of hæmophilia A in girls (Quick and Hussey 1958, Choremis et al. 1956) mentioned earlier are similar to the present case. However, nothing is known about the pedigree in these patients, and determination of cytological sex was not attempted. There is one observation in the literature which strongly indicates a chromosomal situation like that described by us. Walton (1956) in a study of sex-linked muscular dystrophy of the Duchenne type observed one affected girl along with seven males in the same family. The girl's mother was obviously the conductor. The leucocyte sex was of male type.

Our case demonstrates that seeming exceptions from sex-linked inheritance may in reality conform to the genetic pattern that would be expected. It also confirms the correctness of leucocyte sex determinations and chromosome maps, since the single X chromosome found was marked by a sex-linked genetic trait.

This investigation was supported by grants from the Swedish Medical Research Council and from the Swedish Cancer Society.

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MONITORING THE HEART OF THE FŒTUS AND THE NEWBORN

D. J. MACRAE
M.D. Edin., F.R.C.S., F.R.C.O.G.
OBSTETRICIAN AND GYNÆCOLOGIST, THE MOTHERS' HOSPITAL, LONDON E.5, AND TO THE NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD

THERE is urgent need for more frequent recording of fœtal heart-sounds during pregnancy and labour. The significance of many of the changes in fœtal heart-sounds is little understood, and when they cease altogether—for instance, in intrauterine fœtal death associated with maternal diabetes or with toxæmia of pregnancy—it is not known whether asystole was sudden, or whether it was preceded by irregularities in rate and rhythm. During

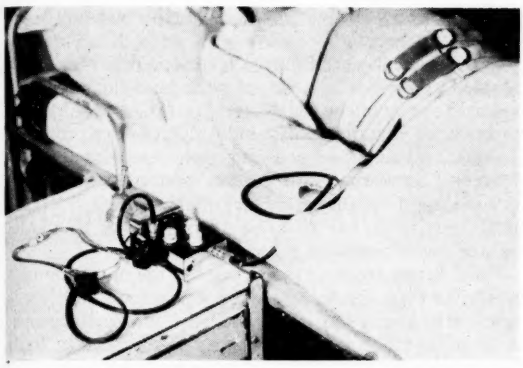

Fig. 1—The ' Thora ' abdominal belt is seen holding the microphone over the anterior shoulder of the fœtus, which lies in the R.O.L. position.

The microphone goes to one of the intake channels of the soniscope, which shows 3 knobs for adjusting the high and low frequencies and the volume. There are two output channels, used separately, one for earphones (shown), and the other for the cardiophone lead.

normal labour the rate and rhythm of the fœtal heart alter with uterine contractions, and at engagement of the fœtal head. In abnormal labour such changes are common in fœtal distress, and not infrequently the first warning of danger to the fœtus is the absence of fœtal heart-sounds.

Unfortunately, with the ordinary fœtal stethoscope, long periods elapse without a check being made on the heart, so that fœtal distress may be well advanced when first discovered. This is especially true where there may be most need of careful observation—e.g., in prolonged labour, in trial of labour, or when the patient is asleep. For the past five years, therefore, I have been trying to discover a means of continuously monitoring the fœtal heart.

The Device

In 1953, Gunn and Wood relayed the fœtal heart-sounds to a loudspeaker, and our efforts have been centred on finding a small microphone which could be worn in comfort by the patient, and would transmit fœtal heart-sounds without interference. Such a microphone is embodied in the ' Soniscope ', as described by Kinnier Wilson, Fothergill, and Selwyn Taylor (1956). It can be worn for long periods and with the patient lying on her side.

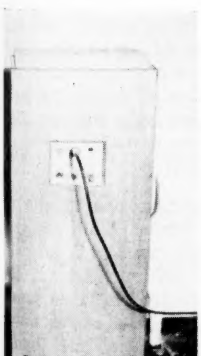

Fig. 2—Cardiophone in the labour-ward office, with the lead to it from the soniscope.

The switch on the right brings the flashing indicator into play. Below the soniscope lead is an outlet channel for earphones.

Immobilisation of the microphone on the abdominal wall, to prevent friction sounds and give adequate pressure, is achieved with the ' Thora ' belt. This is a wide webbing belt with adjustable elastic straps, made originally for the treatment of rib fractures; it can be scrubbed with soap and water.

The microphone is placed on the abdomen over the area where the fœtal heart is best heard, and covered with a pad of gamgee, or plastic rubber, which reduces extraneous sounds. The belt holds the microphone in firm apposition to the abdominal wall, and is tightened to direct the microphone towards the uterus. (This does not interfere with uterine action, but incidentally helps to relieve the patient's backache.)

The microphone is then connected to the soniscope, which selects and amplifies the fœtal heart-sounds, and, by means of earphones, the sounds are tuned to their optimum volume. Another output socket connects up with a loudspeaker. The soniscope can be attached to the foot of the bed, or left on a bedside table (fig. 1), and the loudspeaker can be placed in a corner of the labour ward, or taken to another room (fig. 2). The best loudspeaker is of a type especially made to select the low-frequency fœtal heart-sounds, and its modification to prevent acoustic feedback permits its use in the same room as the microphone. The fœtal heart can thus be heard at any time without disturbing the patient, and continuously monitored by loudspeaker.

Towards the end of the second stage of labour the microphone has usually to be brought to the midline above the pubis, because of rotation of the shoulders, and this allows recordings to be made until crowning of the head.

Some other methods of fœtal-heart recording may be used, employing the soniscope as a pre-amplifier.

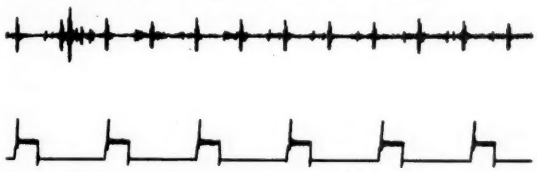

Fig. 3—Phonocardiograph showing both fœtal heart-sounds, the second being more pronounced.

A fœtal kick is seen at the left side of the tracing, which is timed below by a marker (in secs.).

Fœtal heart changes can be shown visually by a red-flashing indicator on the front of the loudspeaker. It is more difficult, however, to become accustomed to visual observation of rate and rhythm.

The fœtal heart may also be heard by means of earphones plugged in to the loudspeaker. This may be useful at night.

Another device is the use of the soniscope to make tape recordings of the heart-sounds. These recordings can be made at set intervals and played back when convenient.

Fœtal heart action may also be recorded phonographically (fig. 3). Besides showing irregularities, this can reveal alteration in systole and diastole times. The cardiophone is being modified to make both sound and phonographic recordings at set intervals by means of an automatic switch.

Another important use of the cardiophone is in monitoring the heart in the newborn.

In the presence of asphyxia the microphone can be fixed over the heart with zinc strapping, and the heart sounds are then heard through the cardiophone while respiration is established.

Where the fœtal heart has been irregular, or the baby's condition poor, a continuous watch can be kept during the first few hours of life.

Discussion

A more exact understanding of the action of the fœtal heart in pregnancy and labour can be gained from continuous monitoring or intermittent graphing of the heart-sounds. In the presence of maternal complications known to predispose to intrauterine death, the twice-daily fœtal-heart check could be replaced by periodic relaying of the sounds to the ward office. With the ordinary fœtal stethoscope frequent checking is hardly practicable, and it would alarm the patient; but cardiophonic recordings permit clinical work to continue while this watch is being kept. If two or three daily phonocardiographic records

are made, heart systole and diastole can be measured to provide an additional guide to heart action, and warning signs of imminent intrauterine fœtal death may be seen. In cases of hypertension, for instance, where intrauterine death is still a major problem (MacRae 1958), the fœtal heart-sounds sometimes disappear before a decision has been reached about the best date for inducing labour.

During labour itself fœtal distress is common, and a more continuous check on the fœtal heart is badly needed. Pitocin-drip induction of labour has been widely adopted; and, instead of the physiological dose and careful technique advocated by Theobald (1959), much stronger pitocin solutions are used, making fœtal distress relatively common. The bottle of 5% glucose solution, which was recommended to replace the pitocin as soon as contractions are well established (MacRae 1952), now contains pethidine in anticipation of uterine hypertonicity and fœtal distress. Clearly in such circumstances there should be continuous monitoring of the fœtal heart.

We have used the cardiophone also in complicated labour—e.g., in patients whose membranes have been ruptured for some time, in patients with cephalopelvic disproportion, and when a continued fœtal-heart check was desirable at night. Frequent disturbance of the patient to check the fœtal heart undoubtedly unsettles and worries her, and adds to the likelihood of uterine inertia; but all this is avoided by relaying the sounds to a loudspeaker in the labour-ward office.

The fœtal heart of a number of patients, simultaneously in the first stage of labour, can readily be checked by having separate microphones and soniscopes, which can be connected to a switch box and thence to the cardiophone. Periodic checking can be carried out in the patient's room by earphones, or by the remote loudspeaker.

During the second stage of labour, when uterine contractions are more powerful and the fœtal brain subject to the stresses of moulding, continuous recording of the fœtal heart-sounds is very reassuring. The effects on the heart are heard throughout the contractions although at times adventitious sounds limit full reception. Fœtal distress may appear suddenly, and its early recognition allows immediate steps to ensure quick delivery. Late diagnosis of the beginning of the second stage of labour is common, since in most cases it is recognised only when the fœtal head is distending the perineum. Strong levator muscles can obstruct the passage of the head before it reaches the perineum and keep it high, and severe cerebral damage may be caused by prolongation of this stage of labour; the warning sign of meconium-stained liquor is often absent because the fœtal head fits the pelvis closely. Intermittent checking can miss the irregular heart action, and it is at this stage that disappearance of fœtal heart-sounds is frequently reported. Continuous monitoring of the fœtal heart therefore appears essential in the second stage of labour.

Tumultuous movements of the fœtus are a sign of its being subject to undue stress, and this is also picked up by the cardiophone. Investigating the reason for this sign in a recent labour, we were surprised to find the cervix fully dilated, with membranes unruptured; we were able to expedite delivery by rupture of the membranes. It is interesting to hear the alterations in the fœtal heart-rate and rhythm under the pressure of a uterine contraction, and the accompanying reflex "kicks" by the fœtus indicate the stress it suffers. Tape recordings of heart-sounds show that their amplitude can greatly decrease during a strong contraction, after which there is a compensatory increase.

Pressure on the head during a forceps delivery is well revealed by the cardiophone; in some cases there is much less irregularity of the fœtal heart than in others, but the cardiophone gives immediate indication of the strength of the traction being used and also of the need for speed in delivery. Similarly, with breech presentation, in the second stage of labour before the cord can be felt, irregular fœtal-heart action has indicated that the breech should be assisted past the levator muscles.

Fœtal hearts are more easily heard if the microphone is kept at an even pressure over the area where the heart is best heard; in this way it simulates the aural stethoscope. If the fœtus tends to move away, its position can be fixed by a lateral pad of gamgee under the webbing belt. This belt is comfortable, and plays a major part in good sound transmission by fixing and directing the microphone. Insulation of both microphone and its lead lessens extraneous interference. The heart-sounds are fundamentally of low frequency, and the deep notes tend to become tedious to the ear; when listening to the harmonics, the higher frequency sounds have to be limited to cut out extraneous noises in the same range. Further experiments are being made to adjust these factors and to secure high amplification.

The cardiophone can play an important part in the resuscitation of the newborn. Failure of the lungs to expand puts a severe strain on the heart, which may remain slow and irregular until opening of the pulmonary circulation, and then become very rapid before it settles down. Not uncommonly, during some minutes' attempt to establish respiration, the condition of the heart is not appreciated, and when eventually listened for heart-sounds may be absent. It would be a great advantage, therefore, to hear the heartbeats while trying to make the baby breathe, and to know when to turn one's attention to the heart should it show signs of failure.

In babies in whom the heart has been irregular during pregnancy or labour, a continuous record by cardiophone, over the first few hours of life, may be valuable; and in recurrent cyanosis continuous monitoring could be maintained.

During exchange transfusion, which always puts a strain on the heart (especially in premature or recently shocked babies, or where there is citrate intoxication) there would be an obvious advantage in hearing the heart-sounds. In a recent case heart irregularity was marked during the withdrawal phases of the exchange. Neither continuous nor periodic monitoring will impede the operation.

Summary

Continuous monitoring of the fœtal heart during labour provides early evidence of fœtal distress. This can be easily achieved with a 'Soniscope' and fœtal cardiophone.

Such monitoring is necessary (*a*) in abnormal labour, (*b*) whenever a pitocin drip is being given, (*c*) in the anxious and sleeping patient, and (*d*) in the second stage of labour.

The cardiophone permits auscultation of the fœtal heart during uterine contraction, giving warning by excessive slowing; it reveals reflex fœtal kicks and tumultuous movements of distress; and during forceps delivery it can guide the strength and duration of traction.

Where complications are suspected during pregnancy, periodic checks by cardiophone (or phonocardiograph) will reveal any disturbance of fœtal-heart action.

In the newborn the cardiophone provides an important guide to the condition of the heart (*a*) when there has been irregularity of the fœtal heart-rate, (*b*) during resuscitation from asphyxia, (*c*) in the presence of recurrent cyanosis, and (*d*) during exchange transfusion.

I should like to thank the North East Metropolitan Hospital Regional Board for a grant towards equipment, and Mr. Lionel Fothergill and Mr. Peter Mason for their assistance. The 'Soniscope' and cardiophone are made by Messrs. Faraday, Electronic Instruments Ltd., 65, Fair View Road, London, S.W.16, who kindly made many modifications for me.

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Preliminary Communications

HYPOGLYCÆMIA INDUCED BY GALACTOSE

A COMPARATIVELY little-known feature of congenital galactosæmia is the fall in blood-glucose which accompanies the rise in blood-galactose (fig. 1). Though the accumulation of galactose-1-phosphate, due to deficiency of a specific enzyme, is generally accepted as the cause of most symptoms of the disease,[1 2] some of its clinical manifestations can be attributed directly to hypoglycæmia.[3–5] These manifestations almost certainly include the occasional death of infants in unrecognised hypoglycæmic coma. We decided to investigate whether this hypoglycæmic effect of galactose is confined to patients with galactosæmia; and if it is not whether it could be of clinical importance outside this syndrome.

EFFECT OF BLOOD-GALACTOSE ON BLOOD-GLUCOSE

A slight fall in blood-glucose has been noted incidentally in some series of galactose-tolerance tests in patients with gastrointestinal and endocrine disease, especially in children [6 7]; and several American workers have suggested that a raised blood-galactose lowers the blood-glucose.[8 9] When the galactose-tolerance test is performed routinely, however, to assess liver function, it is not usual to estimate the total sugar or glucose in addition to the galactose in the blood.[10] In these tests, moreover, the blood-galactose rarely rises sufficiently to lead one to expect a fall in blood-glucose.

The effect of 50 g. galactose by mouth on the blood-glucose levels of 6 volunteers was variable. Venous blood-samples taken every ten minutes showed a transient slight fall in blood-glucose in only 3. After 100 g. galactose by mouth 4 of the same 6 volunteers had a greater but not striking fall in blood-glucose within the first hour.

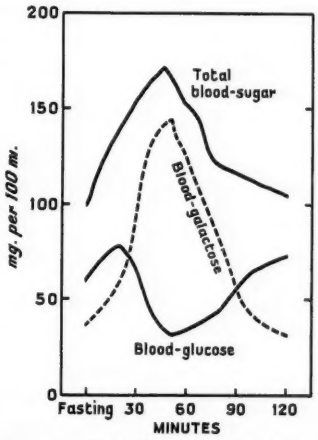

Fig. 1—Total-blood-sugar and blood-glucose curves in a symptomless sibling of a galactosæmic infant after 50 g. galactose by mouth. The interrupted lines shows the "blood-galactose" as calculated from the difference between the total-blood-sugar and blood-glucose levels.

The hypoglycæmic effect of a high blood-galactose could be shown, however, by galactose given intravenously. In all but 1 of 6 volunteers the blood-glucose began to fall within a few minutes of the total-blood-sugar curve reaching its peak; and this depression persisted for up to ninety minutes (table I, fig. 2).

We estimated the blood-glucose by the glucose-oxidase method of Middleton and Griffith [11] and the total blood-sugar by the method of Asatoor and King.[12] Recently Middleton suggested a slight modification of the glucose-oxidase method to overcome the inadequate colour-production with low glucose concentrations [13]: we, too, found the original method unsuited to accurate estimations in the grossly hypoglycæmic range. In all experiments we used standards corresponding to 5, 10, 25, 50, and 100 mg. glucose per 100 ml. and the blood-samples were taken mostly at ten-minute intervals.

In most tests the intravenous galactose was given as a 20% solution—60 g. in 300 ml. water. For rapid administration this requires a blood-transfusion pump. 40% and 60% solutions can be infused more quickly; but they should be given only into large veins, otherwise they may cause a painful phlebitis.

POSSIBLE CLINICAL SIGNIFICANCE

The mechanism whereby blood-galactose influences blood-glucose is unknown. There appears to be some evidence that a rise in blood-galactose directly stimulates the pancreatic islet-cells to secrete insulin [14]; but glucose release by the liver may be influenced as well.[15 16] It would seem that, whatever metabolic processes regulate blood-sugar, maintaining it within comparatively narrow limits, they may not distinguish between glucose and galactose: thus, a sharp rise in blood-galactose will stimulate those mechanisms which depress the total blood-sugar (both blood-glucose and blood-galactose).

Whereas this homœostatic response to a rising blood-

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TABLE I—EFFECT OF GALACTOSE INTRAVENOUSLY ON THE TOTAL-BLOOD-SUGAR (TBS) AND BLOOD-GLUCOSE (Gl) LEVELS OF HEALTHY VOLUNTEERS. SUBJECTS B AND D RECEIVED 40 G. GALACTOSE; SUBJECTS A, C, E, AND F 60 G. GALACTOSE (VENOUS BLOOD SAMPLES)

Subject	—	Time (min.)									
		F	10	20	30	40	50	60	90	120	150
A	TBS	89	345	245	212	160	128	131	105	90	..
	Gl	66	70	51	59	45	69	67	81	86	..
B	TBS	104	310	230	224	219	177	152	124	94	96
	Gl	85	82	59	65	64	75	78	100	89	89
C	TBS	118	368	310	275	242	220	205	151	110	..
	Gl	79	117	52	32	50	48	55	60	94	..
D	TBS	108	295	276	247	213	200	183	107	95	90
	Gl	96	96	85	88	92	102	100	87	80	82
E	TBS	87	357	327	286	247	230	218	157	118	90
	Gl	67	88	43	38	44	52	68	74	76	75
F	TBS	82	351	302	251	180	138	122	80	95	..
	Gl	65	92	58	35	32	46	58	64	72	..

F = fasting.

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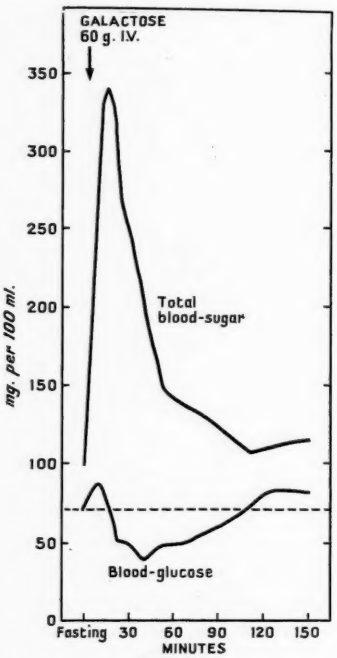

Fig. 2.

Fig. 2—Composite total-blood-sugar and blood-glucose curves in 6 volunteers after 60 g. (respectively 40 g.) galactose intravenously.

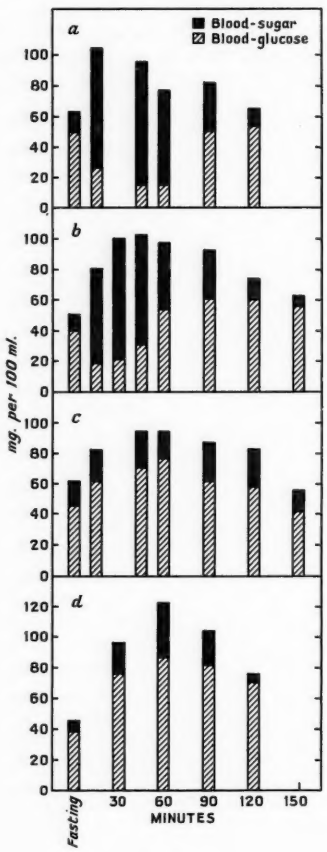

Fig. 3.

Fig. 3—Total-blood-sugar and blood-glucose levels in a premature infant (case 3) after test-feeds:

(*a*) *2nd day* (1st milk-feed). Wt. 6 lb. 3/4 oz. Serum bilirubin 13 mg. per 100 ml. Feed: 4 drachms expressed breast milk (E.B.M.)≡1 g. lactose≡0·16 g. per lb. body-weight.

(*b*) *3rd day* (4th milk-feed). Two cyanotic attacks since test-feed (*a*), not apparently related to feeds: spontaneous recovery from each. Baby lethargic, jaundiced ++. Feed: 6 drachms E.B.M.≡0·24 g. per lb. body-weight.

(*c*) *10th day*. Wt. 6 lb. 1 1/2 oz. Staphylococcal conjunctivitis; otherwise progressing well; jaundice clearing. Feed: 1 1/2 oz. E.B.M.≡0·45 g. per lb. body-weight.

(*d*) *20th day*. Wt. 6 lb. 8 oz. Staphylococcal infection cleared. Serum-bilirubin 3 mg. per 100 ml. Feed: 2 oz. E.B.M.≡0·58 g. per lb. body-weight.

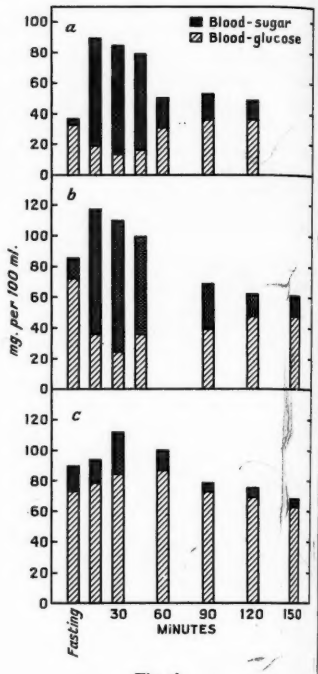

Fig. 4.

Fig. 4—Total-blood-sugar and blood-glucose levels in a premature infant (case 7) after test-feeds:

(*a*) *3rd day* (4th E.B.M. feed). Wt. 6 lb. Serum-bilirubin 10 mg. per 100 ml. Feed: 1 oz. E.B.M.≡2 g. lactose≡0·3 g. per lb. body-weight.

(*b*) *4th day* (9th feed). Feed: 1 1/2 oz. E.B.M.≡0·45 g. per lb. body-weight.

(*c*) *9th day*. Wt. 6 lb. 2 oz. Serum-bilirubin 8 mg. per 100 ml. Feed: 2 oz. E.B.M.≡0·6 g. per lb. body-weight.

sugar is relatively non-specific, strong evidence suggests that many tissues—notably nerve-cells—cannot metabolise galactose or other sugars in place of glucose.[17 18] Normally they are not required to do so. Galactose does not usually represent more than a fraction of the total blood-sugar: it is rapidly converted to glycogen and glucose in the liver; and what is not converted is excreted in the urine. (Unlike glucose, galactose is a low-threshold or no-threshold substance). It occurred to us, however, that under certain abnormal or exceptional conditions the blood-galactose might rise to a sufficiently high level and stay there for long enough to depress blood-glucose. Routine laboratory methods of " true-sugar " estimations would not detect this hypoglycæmia since they estimate both glucose and galactose (as well as some other sugars).

The conditions which seem to us to warrant investigation in particular are the neonatal period (especially of premature infants) and the complications of pregnancy.

Pregnancy

In pregnancy factors which merit a-priori consideration include the low renal threshold for glucose, the conversion of glucose to galactose in the lactating breast, and possible impairment of liver function. Preliminary experiments suggest, moreover, that non-glucose sugars constitute a higher than normal fraction of the total blood-sugar in pregnancy.

Newborn Infants

In the neonatal period lactose is the chief carbohydrate food; and liver function may be much less efficient than in the normal adult.[19 20] A preliminary investigation was carried out on 6 premature and 3 full-term infants.

Galactose-tolerance tests—both oral and intravenous—have been performed on newborn babies; but for our purpose they did not seem justified. Such tests, moreover, do not reproduce the clinical conditions in which we are interested (except, possibly, those of congenital galactosæmia). We felt, on the other hand, that the infant's ordinary feed could be regarded as a rough-and-ready combined glucose-galactose tolerance test. The approximate sugar content of expressed breast-milk is known: and the amount of galactose and glucose given can be calculated and expressed in mg. per lb. body-weight.

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TABLE II—EFFECT OF 15 "TEST-FEEDS" OF EXPRESSED BREAST-MILK ON THE TOTAL-BLOOD-SUGAR (TBS) AND BLOOD-GLUCOSE (Gl) LEVELS OF 7 PREMATURE AND 2 FULL-TERM NEWBORN INFANTS (CAPILLARY BLOOD SAMPLES)

No.	Weight	—	Time (min.)								
			F	15	30	45	60	75	90	105	120	150
1	6 lb. 3 oz.	TBS	52	68	66	60	58	50	48	..	140	32
		Gl	44	48	52	52	50	45	40	..	36	31
2	Full-term	TBS	47	58	69	80	93	..	82	..	48	55
		Gl	41	48	54	60	64	..	60	..	48	49
3	6 lb. 3/4 oz.	TBS	61	92	..	83	75	..	78	..	62	..
		Gl	47	26	..	15	16	..	50	..	52	..
	..	TBS	50	78	96	98	95	..	89	..	70	61
		Gl	40	19	22	30	53	..	60	..	58	54
	..	TBS	60	81	..	89	91	..	84	..	79	53
		Gl	45	60	..	71	75	..	60	..	57	46
	6 lb. 8 oz.	TBS	44	..	94	..	109	..	104	..	76	..
		Gl	39	..	75	..	86	..	80	..	70	..
4	6 lb. 1 1/2 oz.	TBS	39	46	60	..	72	..	68	..	58	..
		Gl	35	36	53	..	61	60	60	..	52	..
5	Full-term: jaundiced ++	TBS	70	..	90	96	84	..	70	..	68	..
		Gl	50	..	48	44	56	..	50	..	49	..
		TBS	71	..	90	..	85	..	68	..	54	50
		Gl	38	..	41	65	65	..	54	..	46	46
6	Full-term: jaundiced +	TBS	44	58	60	64	70	68	60	51	47	43
		Gl	40	48	53	49	51	50	48	46	39	37
7	6 lb.	TBS	34	85	80	75	47	..	50	..	46	..
		Gl	32	18	13	16	29	..	34	..	35	..
	..	TBS	81	109	104	94	..	..	64	..	59	58
		Gl	69	33	23	34	..	..	38	..	46	45
	6 lb. 2 oz.	TBS	85	89	106	..	94	..	74	..	71	64
		Gl	70	75	80	..	83	..	70	..	67	60
8	6 lb. 1 oz.	TBS	35	38	41	43	52	42	40	40	30	32
		Gl	28	28	20	17	18	20	25	26	27	30
9	6 lb. 1/2 oz.	TBS	43	..	51	57	57	..	32	..	32	..
		Gl	28	..	32	..	47	..	30	..	31	..

From the results of the "feed tests" only a general pattern emerges (table II); but it is noteworthy that in cases 3 and 7—both premature and jaundiced infants—the initial and early milk-feeds precipitated a fall instead of a rise in blood-glucose (figs. 3 and 4). Repeat tests during the first few weeks showed a gradual reversal of this phenomenon and the emergence of normal response. Neither of these infants showed definite clinical signs of hypoglycæmia: this was, in fact, brief and mild, considering the tolerance of infants to fluctuations in blood-sugar.[21–26] We would not exclude the possibility, however, that hypoglycæmia induced by lactose or galactose is an occasional clinical as well as a biochemical feature of the neonatal period. Such hypoglycæmia—even if severe, prolonged, and repeated—would not be revealed unless estimations were carried out specifically for glucose: routine sugar estimations could give normal or even high figures.

We are grateful to Miss Gladys Hill, Prof. K. R. Hill, and Dr. D. N. Baron, of the Royal Free Hospital, for their help, and both to them and to the Director of Army Medical Services for permission to publish.

Department of Pathology, Royal Free Hospital, London, W.C.1 — THOMAS L. DORMANDY, M.B., B.SC. Lond., F.R.C.S.E.

British Military Hospital, Rinteln — DAVID LEAK, M.B. Edin., M.R.C.P.E.

Department of Gynæcology and Obstetrics, Royal Free Hospital — MICHAEL GRANT, M.B. Lond., M.R.C.O.G.

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TRANSFER OF IRON TO PROTOPORPHYRIN FOR HÆM BIOSYNTHESIS

ROLE OF ASCORBIC ACID AND GLUTATHIONE

HÆM biosynthesis is essential for the formation not only of hæmoglobin but also of the cytochromes, catalase, and the peroxidases. It takes place in many tissues of the body.[1] The iron it requires is transported in the plasma by siderophilin (a β_1-globulin) and is stored throughout the reticuloendothelial system, in the proteins ferritin and hæmosiderin. But there is still doubt about the mechanism whereby the iron, transported or stored in these proteins, is transferred to protoporphyrin for hæm biosynthesis. Mazur et al.[2] have shown that certain reducing substances, including ascorbic acid and reduced glutathione (G.S.H.), release ferrous iron from ferritin. Our previous work [1 3] has demonstrated that ascorbic acid and G.S.H. influence the enzymic incorporation of iron into hæm by an extract of avian erythrocytes or of certain human or rat tissues. Rat-liver mitochondria are a rich source of this iron-incorporating enzyme system, the activity of which is greatly increased by the addition of ascorbic acid or G.S.H.[1] The iron used in these studies was in the form of $^{59}FeCl_3$.

Further experiments have been undertaken to determine whether these reducing substances render protein-bound iron available for hæm biosynthesis.

METHODS

Radio-iron (^{59}Fe) was incorporated into rat plasma and liver and human serum by the following methods.

Young female albino rats, weighing 150–200 g., were each injected intraperitoneally with about 50 μC of $^{59}FeCl_3$ and 2500 units of heparin. After one hour the animals were anæsthetised with ether and killed by exsanguination; the blood was collected and spun at 2500 r.p.m. for 15 minutes. The separated plasma had a specific activity of about 1 μC per ml. The liver was perfused through the portal vein with 20 ml. physiological saline solution to remove trapped plasma and was then excised and homogenised in ice-cold 0·25*M* sucrose to a 20% homogenate. This homogenate, after dialysis against ion-free water for about 20 hours, had a high specific activity (about 0·5 μC per gramme of tissue) of protein-bound radio-iron. Human serum was incubated with radio-iron for one hour at room temperature. The serum-iron concentration and total iron-binding capacity had been determined and enough $^{59}FeCl_3$ (specific activity 1–3 μC per μg. of iron) was added to the serum sample to fully saturate the iron-binding protein.

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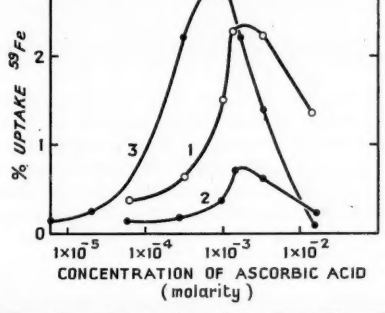

Fig. 1—Effect of varying concentrations of ascorbic acid on the transfer of iron from human siderophilin (1), rat siderophilin (2), and rat-liver homogenate (3) to protoporphyrin for hæm biosynthesis.

COMPARISON OF ASCORBIC ACID AND G.S.H. CONCENTRATIONS OF HUMAN AND RAT LIVER (μG. PER G.) WITH THE CONCENTRATIONS OF THESE SUBSTANCES WHICH WERE EFFECTIVE IN VITRO (μG. PER ML.)

Ascorbic Acid	Human liver	58 (±22)
	Rat liver	214 (±11)
	Effective range in vitro	50–1600
	Optimal concentration in vitro	200–700
Reduced Glutathione	Human liver	1790 (±610)
	Rat liver	2260 (±340)
	Effective range in vitro	200–5000
	Optimal concentration in vitro	2000

Each sample of plasma or serum and dialysed liver homogenate was ultrafiltered [3] for 3-6 hours at 76 cm. Hg pressure to ascertain that all the radio-iron was protein-bound. In no case was more than 0·5% of the iron ultrafilterable.

Serum samples were subjected to paper electrophoresis for 16 hours at 1·2 milliamps current in a barbitone buffer pH 8·6, and the paper strip was scanned for radioactivity. The radioactivity resided in the β-globulin fraction, suggesting that the radio-iron was bound to siderophilin.

The method of estimating hæm formation was that detailed by Goldberg.[3]

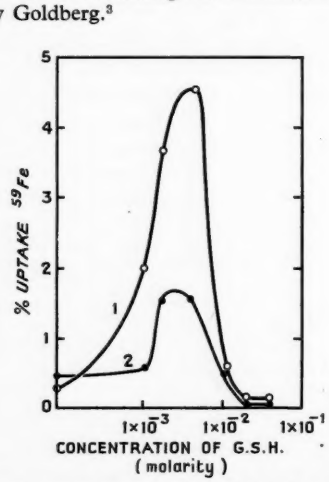

Fig. 2—Effect of varying concentrations of G.S.H. on the transfer of iron from rat-liver homogenate (1), and human siderophilin (2), to protoporphyrin for hæm biosynthesis.

This consists essentially in incubation for 3 hours of ^{59}Fe with protoporphyrin and a preparation containing the iron-incorporating enzyme system at 37°C and pH 7·4. Purified crystalline hæm is then isolated, and the quantitation of the specific activity of the hæm (count rate per mg.) gives an accurate measure of new hæm synthesised.

In the present studies the radio-iron used was either bound to rat-liver proteins or to rat plasma or human serum. When ^{59}Fe bound to liver proteins was used, the liver homogenate served as both a source of ^{59}Fe and of iron-incorporating enzyme. When ^{59}Fe bound to plasma or serum was used, the source of iron-incorporating enzyme was rat-liver mitochondria, prepared by the method of Schneider.[4] In all the experiments, protoporphyrin ($2\times10^{-5}M$) was added to each incubation flask.

RESULTS

Under these conditions, some hæm formation occurred enzymically when either serum or liver protein-bound iron was used as an iron source. This formation was considerably increased when ascorbic acid or G.S.H. was added to each system. Fig. 1 shows the effect of varying concentrations of ascorbic acid on the incorporation into protoporphyrin of iron transferred from human and rat siderophilin and from rat-liver homogenate. The influence of G.S.H. is shown in fig. 2.

Ascorbic acid ($1-4\times10^{-3}M$) and glutathione ($5-7\times10^{-3}M$) were the optimal concentrations in these experiments, whether the iron source was human serum or rat plasma or liver. The effective ranges of ascorbic acid and G.S.H. are such as occur normally in human liver or rat liver (see table).

Since iron is stored in the liver within the proteins ferritin and hæmosiderin, the results suggest that ascorbic acid and G.S.H. take part in the transfer of iron from these proteins for hæm biosynthesis. These substances also influenced the transfer of iron from rat and human siderophilin to protoporphyrin. In most of the latter experiments the source of the iron-incorporating enzyme system was rat-liver mitochondria. In one experiment in which the radio-iron was bound to human siderophilin, the enzyme system was derived from human-liver mitochondria. Ascorbic acid and G.S.H. concentrations were determined [5,6] in nine human livers obtained at necropsy performed within 24 hours of death, and also in ten rat livers. In none of these cases was there evidence of hepatic disease. The concentrations of ascorbic acid and G.S.H. which facilitated the transfer of iron from these proteins were within the ranges of those which occur in human as well as rat liver (see table). These facts suggest that our results have a relevance to human physiology.

This work was aided by a grant from the British Empire Cancer Campaign.

ANN C. LOCHHEAD
B.SC. Glasg.
A. GOLDBERG
M.D. Edin., M.R.C.P., F.R.F.P.S.

University Department of Medicine,
Gardiner Institute,
Glasgow, W.1

POLIOVIRUS-NEUTRALISING ANTIBODY IN FÆCES OF POLIOMYELITIC CHILDREN

THE information which follows is presented now because of (*a*) a growing recognition that Salk-vaccinated people when infected, shed poliovirus freely in their fæces even if their serum antibody titre is high, whilst children infected naturally or fed attenuated polioviruses artificially show relative resistance to alimentary homotypic virus multiplication[7]; (*b*) the prevailing interest in combinations of peripheral Salk and/or oral vaccination for poliomyelitis; and (*c*) the desirability that other investigators should confirm and extend our findings in children who may become infected in the next few months, by examining fæcal specimens late in convalescence.

We demonstrated poliovirus antibody in the stools of 13 children with poliomyelitis (paralytic or nonparalytic).

The stools were prepared simply as 20% suspensions for viral isolation, and then heated at 56°C for an hour to destroy viral infectivity without affecting neutralising antibody. Standard neutralisation tests were conducted in suspended cell-tissue cultures, with appropriate controls for cells, the three virus serotypes, and the type-specific antisera; end-points were read by colorimetric and cytopathogenic techniques.

The nature of the antibody and specificity of the

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5. Roe, J. H., Kuether, C. A. *ibid.* 1943, **147**, 399.
6. Woodward, G. E., Fry, E. G. *ibid.* 1932, **97**, 465.
7. Sabin, A. B. *Brit. med. J.* 1959, i, 663.

EXAMPLES OF FÆCAL ANTIBODY TO EACH OF THE THREE SEROTYPES OF POLIOVIRUS

Case no.	Clinical state	Titre demonstrated		
		Vs. type	Fæces	Serum
1	Paralytic	1	1/80*	1/512
2	Paralytic†	2	1/80*	1/2048
3	Non-paralytic†	3	1/160*	1/512

* Based upon the 20% suspensions tested against 100 TCD_{50} of virus.
† Type 1 fæcal virus isolated in vitro.

neutralisation observed in the 13 children is shown by the following:

(*a*) Thermostability at 56°C for one hour; (*b*) concentration by ammonium-sulphate precipitation; (*c*) it is type-specific rather than inhibitory (in 12 out of 13 children neutralisation of a single virus type, in 1 child neutralisation of two types); (*d*) when present in the fæces the corresponding type(s) of antibody is present also in the serum; and (*e*) reproducibility of results with the same frozen fæcal specimen when thawed and retested.

Since the fæcal antibody observed is heterotypic to the children's current poliovirus infection, it would be of considerable value to follow virus excretion, and stool and serum-antibody levels, of individual patients for a long time.

Thus, case 1 (type-1 paralytic poliomyelitis) had nine serial examinations for stool and serum-antibody in the first seven weeks of illness; longer follow-up would have been helpful but was impossible. Despite previous Salk vaccination (3 ml.) she shed in the stools type-1 poliovirus throughout the seven weeks, in which time type-2 antibody developed in her fæces (from negative on the fifth day to a dilution of 1/80 versus 100 TCD_{50} of type-2 poliovirus on the twenty-first day of illness). Serum-antibody to both type 1 and 2 were present; at no time during this period of observation did type-3 antibody appear in either her stools or serum.

Representative examples of fæcal antibody to each of the three serotypes of poliovirus are shown in the table.

The heterotypic response of some of the patients was first shown in earlier in-vivo studies designed to elucidate the serum-antibody response in human poliomyelitis.[8] The heterotypic neutralising antibody response observed in serum is delayed and transitory [9 10] when compared to the homotypic response. Complete understanding of the mechanism and meaning of the heterotypic local response requires further study; meanwhile investigators attempting to duplicate these findings should test simultaneously against all three serotypes of poliovirus rather than the type shown (or epidemiologically assumed) to be responsible for the current infection.

A possible explanation is that alimentary exposure to a single serotype of poliovirus sensitises appropriate local cells to group-specific as well as to species-specific antigens. Heterotypic local antibody may thus be expected to appear, especially if the same alimentary tract has had previous experience with that heterotypic poliovirus.

Tests for complement-fixing poliovirus antibody in stools are being developed. We plan ultimately to conduct and report fully longitudinal studies of the stools of poliomyelitis patients, and we hope other investigators will have similar opportunity. The possible importance in relation to routes of immunisation for controlling the spread of poliovirus as well as disease is apparent.

ALEX J. STEIGMAN
M.D., M.SC., HON. D.SC. Temple
M. M. LIPTON
B.A., M.SC., PH.D. Michigan
Department of Pediatrics and Kentucky Child Health Research Foundation Laboratory, University of Louisville, Kentucky, U.S.A.

8. Steigman, A. J., Sabin, A. B. *J. exp. Med.* 1949, **90**, 349.
9. Lennette, E. H., Schmidt, N. J. *Amer. J. Hyg.* 1957, **65**, 210.
10. Sabin, A. B. *J. exp. Med.* 1952, **96**, 99.

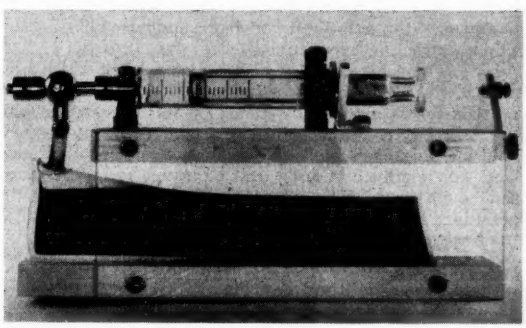
New Inventions

AN OXYGEN ANALYSER

FOR analysis of the oxygen content of the air in tents and incubators we have been using a modification of the apparatus described by Gairdner.[1]

The apparatus consists of a well lubricated syringe, a 3-way tap, and a bag of capacity 40–50 ml. made from flexible polyvinyl chloride (P.V.C.). The upper and lower shelves of the apparatus, upon which rest the syringe and bag, are separated by pieces of 'Perspex' (see figure).

The oxygen-absorbing reagent (10% 1 : 2 : 4-triacetoxybenzene in 15% potassium hydroxide [2]) is contained in the flexible bag. In use, the tap is turned so that the syringe communicates with the bag, and (by carefully withdrawing the plunger of the syringe) the reagent is drawn up until it stands against a mark on the vertical tube. The tap is now turned so that the syringe communicates with the entry nozzle and a sample of the gas to be analysed is drawn into the syringe through a suitable connection. The plunger of the syringe is drawn back against the adjustable stop (which can be seen on the right of the photograph) so that exactly 5 c.cm. of gas is drawn into the syringe. The tap is now turned so that the syringe communicates with the plastic bag and the sample of gas is displaced into it. By tilting the whole apparatus the gas bubble is moved from end to end of the bag: after twelve or more oscillations the bubble is returned to the end of the bag



nearest the tap, and is once more drawn back into the syringe until the absorbing reagent stands precisely at the mark. The contraction in volume, measured on the syringe, represents the concentration of oxygen in the gas sample.

The analyser is, of course, suitable only for rough estimation but it can readily indicate the concentration to within 5%. Although polyvinyl chloride allows slow passage of oxygen we have found that the reagent retains active oxygen-absorbing powers for two months' storage in the bag.

Readers interested in this gadget may write to Messrs. Peacock, 22–28, Collingwood Street, Newcastle upon Tyne, 1.

E. A. PASK
O.B.E., M.D., F.F.A. R.C.S.

1. Gairdner, D. *Lancet*, 1956, i, 786.
2. Devey, J. D. *Scand. J. clin. Lab. Invest.* 1953, **5**, 104.

Reviews of Books

Sympathectomy

An Anatomical and Physiological Study with Clinical Applications. P. A. G. MONRO, M.D., M.SC., lecturer in anatomy in the University of Cambridge, and clinical assistant to the neurosurgical department, The London Hospital, London: Oxford University Press. 1959. Pp. 290. 75*s*.

THE sub title accurately indicates the scope of this book, which embodies the results of much patient investigation over a period of ten years into the effects of sympathectomy on sweating and blood-flow. It is dedicated to a student who died from malignant hypertension, and had shown much interest in the investigations made and the operations performed on herself, and when death approached requested that a further examination be performed afterwards should this be required to complete the research. The book consists of three parts and an appendix; part one deals with sweating after sympathectomy; part two with the autonomic pathways to special areas; part three with vasomotor control after sympathectomy; and the appendix describes the apparatus used, including the methods of its construction, to obtain the observations which constitute the text. The highlight of the book is perhaps the account of the lumbar intermediate ganglia first described by Wrete in 1934 and since investigated in detail by the author in collaboration with Prof. J. D. Boyd.

Certain problems connected with the sympathetic system are dealt with at some length (e.g., nearly 20 pages of text are given to the question of gustatory sweating, the auriculotemporal syndrome, and allied phenomena). While the effect of sympathectomy on the sudomotor and to a slightly less extent the vasomotor pathways is considered in much detail, no attention is given to certain questions, such as the influence of the sympathetic and the effects of its removal on the pharyngeal plexus, the renal pedicle, and the sphincters generally. The case-histories do not mention the age and sex of the patient—an unfortunate omission since age is highly important in questions of regeneration—and the historical introductions to the sections omit much which, though of negative value, has added to our knowledge of the autonomic system. But these are comparatively minor criticisms. Dr. Monro has shown us how sympathectomy can be made more complete and why some surgical procedures have given variable or disappointing results; but time has justified the waning of enthusiasm for the operation and it is unlikely that it will be revived for hypertension.

Here is an achievement of high academic merit which adds particularly to knowledge of the sudomotor and vasomotor functions of the autonomic system. No-one will disagree with Professor Boyd's comment in a foreword that it is the best available account of the long-range effect of sympathectomy. The book is printed in easily read, clear type and is illustrated and bound to the high standard which we expect from the publishing house from which it comes.

X-ray Diagnosis of the Alimentary Tract in Infants and Children

E. B. SINGLETON, M.D., director of radiology, Texas Children's and St. Luke's Hospitals, Houston. Chicago: Year Book Publishers. London: Interscience Publishers. 1959. Pp. 352. 83*s*.

THIS is a clearly written and well-illustrated little book. The author has set out to present the reasons for radiological investigation, a sound technique for carrying out the investigations required, and a description of the disorders that may be found. He has contrived to do this in a readable and interesting fashion. Many interesting illustrative cases—for example, of transitory small-bowel intussusception, and of pneumatosis intestinalis with gas in the portal veins—make the book of value to the doctor with especial interest in, and knowledge of, gastrointestinal radiology. It is a pity some of the illustrations (which are of excellent quality) are printed in reverse so that films taken in the prone position appear as though taken supine. Apart from this the work can be recommended to all interested in the subject.

Frontiers in Cytology

Editor: SANFORD L. PALAY, department of anatomy, Yale University, New Haven. Yale University Press. 1958. London: Oxford University Press. 1959. Pp. 708. 78*s*.

THIS volume consists essentially of a group of lectures given to preclinical students at Yale University in 1955, in memory of Dr. Henry Bunting. The work does not claim to give a complete picture of current trends in cytology, but rather to reflect the varied interests of the contributors. The articles are clear and offer a balanced view of the subjects. Bloch's section on nucleoproteins during the cell cycle, Duran-Reynals' on the ground substance, and Fawcett's on specialisations of the cell surface are examples of difficult subjects dealt with in a readable way. There are over two hundred and fifty photomicrographs. This book can profitably be read by medical students, pathologists, and even clinicians.

Abnormal Hæmoglobins

A Symposium Organised by C.I.O.M.S. Editors J. H. P. JONXIS, State University, Groningen, Holland, and J. F. DELAFRESNAYE, C.I.O.M.S., Paris. Oxford: Blackwell Scientific Publications. 1959. Pp. 427. 45*s*.

IN September, 1957, the Council for International Organisations of Medical Sciences organised at Istanbul a conference on the hæmoglobinopathies to which most workers in this field were invited. This volume records in full the papers given on this occasion. But it is much more than a record of proceedings. The papers are divided into the two main sections—"biological considerations" and "the geography of hæmoglobins." The first section includes papers on identification techniques, clinical and hæmatological aspects of hæmoglobin syndromes, and genetics. The second section starts with a paper by H. Lehmann on the distribution of human hæmoglobin variants, and there follow papers on hæmoglobinopathies in various parts of the world. A copy of this useful and informative guide, which brings together much information that is scattered through many journals, should be found on every hæmatological reference shelf.

The Barbiturate Withdrawal Syndrome

A Clinical and Electroencephalographic Study. MUNKE HERTEL WULFF, department of psychiatry and institute of neurophysiology, University of Copenhagen. Suppl. no. 14 of *Electroencephalography and Clinical Neurophysiology*. Copenhagen: Munksgaard. 1959. Pp. 173. Kr. 28.

THIS monograph gives some useful information about a common and numerically important subject. Of the seventy-eight patients whose records form the basis of the book all could be regarded as barbiturate addicts. Some degree of addiction is widespread, particularly in the United States. When patients who have long been treated with large doses of barbiturate are denied the drug, severe withdrawal symptoms, including fits, may develop. Electroencephalogram changes are also common and may be gross. Symptoms may be so severe as to require resumption of the drug with gradual controlled withdrawal. The pathophysiology of withdrawal symptoms is still not clear; but it seems evident that they are associated only with those forms of barbiturate which are rapidly eliminated. The more slowly eliminated ones are therefore better, *ceteris paribus*, for chronic therapy.

Proceedings of the Fourth International Congress of Biochemistry, Vol. XIV (London: Pergamon Press. 1959. Pp. 299. 75*s*.).—This volume contains the lectures given at the plenary sessions and summaries of the symposia; and Dr. W. Auerswald and Dr. O. Hoffmann-Ostenhof, the editors, suggest that the general reader will find in it a useful review of the "unprecedented amount of scientific material" offered at this congress in Vienna last year. The other 14 volumes are to give a complete account of the proceedings.

THE LANCET
LONDON 5 SEPTEMBER 1959

Blood Disorders in Infancy

THE study of blood diseases in children has always been known to present difficulties not met with in adults. The blood-forming tissues of children are much more labile, and variations that would be pathological in adults are not so in children—for example, the relative lymphocytosis which often occurs normally between the ages of 2 and 5 years and which can be reflected in a lymphocytosis in the bone-marrow sufficient, in an adult, to suggest lymphatic leukæmia. Nowadays the average normal ranges for blood-counts and indices are well established and listed in the textbooks, and, taking these into account, there are few blood diseases strictly limited to children. (Fanconi's familial hypoplastic anæmia is one.) In infancy, however, there are special conditions not present in adult life: antenatal influences may cause trouble, and there are the circumstances attending separation from the mother.

In a recent issue of the *Journal of Pediatrics* devoted to the hæmatology of early infancy EDITH POTTER,[1] of Chicago, points out that most blood conditions causing symptoms in early infancy are due to lack of red blood-cells, and this may be the result of deficient formation, loss by hæmorrhage, or abnormal destruction. The lowest level of hæmoglobin considered normal in infants is higher than the adult normal; POTTER accepts figures of 15·0 g. per 100 ml. for capillary blood or 13·0 g. for venous blood—levels below these indicate " anæmia ". Abnormal destruction is the commonest cause of anæmia in infancy, and the well-recognised Rh-group incompatibility between mother and child is the commonest cause of abnormal destruction. Sometimes the condition is due to ABO incompatibility; and some of the rare groups, such as Kell and Duffy, have also been involved. Exchange transfusion is now the accepted treatment for hæmolytic disease of infancy, and is of course much more successful than in adult anæmias, since birth cuts off the supply of antibody. ERLANDSON and HILGARTNER [2] mention some other causes of hæmolytic disease. Congenital spherocytosis can often be detected in the first few months of life if one remembers that at this stage the fragility of red cells in saline is normally less than in the adult. ERLANDSON and HILGARTNER do not recommend splenectomy in infancy and prefer supportive blood-transfusion if necessary until the child is at least some months old. Fœtal hæmoglobin, which forms 70–80% of the hæmoglobin at birth, is mostly replaced by the adult form by the end of the third month; but ability to synthesise adult hæmoglobin is defective in thalassæmia, a disease that is often recognised by the sixth month and sometimes as early as the third. Sickle-cell disease, also characterised by an abnormal hæmoglobin, can also be detected in the first few months of life. Toxic hæmolytic anæmia sometimes appears in infancy, and Heinz bodies can be found in the blood in this condition [3]; young infants are very susceptible to sulphonamides, and diaper dyes and skin lotions containing resorcin have also been responsible.

Loss of blood by hæmorrhage has proved hard to trace. GUNSON [4] found that fœtal blood can be lost into the maternal circulation, maybe through gaps in the placental barrier, but the mechanism is not clearly understood. ZIPURSKY et al.[5] have shown how these fœtal red cells can be identified in the maternal circulation. This type of bleeding stops as soon as the cord is tied, and, if red-cell formation is active, the blood-level soon rises; so transfusion is not recommended unless the hæmoglobin is less than 8 or 9 g. per 100 ml. Coagulation disorders can also cause loss of blood in infancy. VAN CREVELD [6] recalls that the one-stage prothrombin-time test in infancy normally indicates a concentration of only 14–30% of adult levels; the level slowly rises to full concentration in about a year. The long prothrombin-time in infancy is nowadays attributed to lack of factor VII; and hæmorrhagic disease of the newborn, which is corrected by giving vitamin K, is due to a temporary failure of the liver to produce this factor. Melæna neonatorum is intrauterine melæna associated with failure of the liver to produce yet another clotting factor—factor V. Very occasionally the congenital clotting defects such as hæmophilia and Christmas disease cause clinical signs in infancy. Thrombocytopenia does arise in infancy, but KAPLAN [7] states that it is nearly always due to a maternal anti-platelet antibody and is therefore a self-limiting condition.

There are several known causes of defective blood formation in infancy. CARL SMITH [8] describes the pure red-cell aplasia—apparently a developmental defect—that is particularly conspicuous in infancy and early childhood; the bone-marrow has less than 2% of erythroblasts but all other cell types are normal. Blood-transfusion, administration of steroids, and even splenectomy have been used, and a few remissions have been recorded; but the disease is eventually fatal, and transfusional siderosis of the liver seems to be a special hazard. On the question of iron deficiency in infants NATHAN SMITH [9] draws attention to the odd mechanism whereby iron is transferred from a relatively low concentration in the mother to a relatively high concentration in the fœtus. Iron-deficiency anæmia in the mother is reflected in reduction of the hæmoglobin mass available to the infant at birth, and prematurity has the same effect. The infant needs a good store of iron to start with, since milk contains insignificant amounts. In the first six months infants (American ones, that is) depend for 80% of their iron on iron-enriched infant cereals,

1. Potter, E. L. *J. Pediat.* 1959, **54**, 552.
2. Erlandson, M. E., Hilgartner, M. *ibid.* p. 566.
3. Gasser, C. *ibid.* p. 673.
4. Gunson, H. H. *ibid.* p. 602.
5. Zipursky, A., Hull, A., White, F. D., Israels, L. G. *Lancet*, 1959, i, 451.
6. van Creveld, S. *J. Pediat.* 1959, **54**, 633.
7. Kaplan, E. *ibid.* p. 644.
8. Smith, C. H. *ibid.* p. 609.
9. Smith, N. J. *ibid.* p. 654.

and for the remaining 20% on vegetables, fruit, meat, and eggs. A poor start, gastroenteritis, hæmorrhage, or infection all reduce the iron available or absorbed; so iron-deficiency anæmia is not uncommon in infancy. Whenever possible oral treatment is best, and should be given as a liquid preparation of a ferrous salt; no other substances such as cobalt, molybdenum, or vitamin B_1—still less folic acid or vitamin B_{12}—have been proved to be of the slightest value. If, for any reason, iron cannot be given by mouth, a dextran-iron preparation can be given intramuscularly.

The megaloblastic anæmia of infancy appears rather later—most commonly in the seventh or eighth month, but there have been instances up to seventeen months. The clinical picture [10] is failure to gain weight, anæmia, reduced resistance to infection, hæmorrhagic phenomena, and a more severe illness than the anæmia warrants. The diagnosis is usually made by finding megaloblasts in the bone-marrow—though, being often "intermediate" or "transitional", they may not be easy to detect—and recently examination of the urine for excessive excretion of formiminoglutamic acid has been used in diagnosis.[11] The anæmia responds promptly to the administration of 10–30 mg. of folic acid daily, usually by mouth but intramuscularly if necessary.

Premature infants are especially liable to anæmia, and SCHULMAN [12] has distinguished three stages. From birth to about seven weeks old there is a steady fall of hæmoglobin to rather less than 10 g. per 100 ml. (this stage is due to a temporary diminution of erythropoiesis and shortened life-span of the red cells produced, and iron accumulates in the body stores); in the intermediate stage the hæmoglobin level remains steady or rises a little, erythropoiesis is resumed, and the accumulated iron is used up (this stage also lasts about seven weeks but the period depends on the size of the iron store); in the late stage there is a further decrease in hæmoglobin. This is an iron-deficiency anæmia, and unless iron is given it may persist into the second year.

Leukæmia in the newborn is very rare [13]; only 45 cases in the literature have sufficient evidence to be accepted, and at the Chicago Lying-In Hospital there was only 1 authenticated case in the period 1948–58 among 36,529 babies. No case has been reported in which the mother had leukæmia during the pregnancy. No treatment seems to be even temporarily effective.

The Fuel of Muscular Exercise

THE nature of the fuel utilised by working muscles is an old physiological problem. It has attracted fresh attention by the recent interest in the non-esterified fatty acids in the plasma, commonly known as N.E.F.A. (they are also sometimes referred to as unesterified fatty acids or U.F.A.). It has long been known that about 10% of the fatty acids in the plasma appears on analysis to be in a free state or at least uncombined with glycerol, cholesterol, or any other alcohol; but it was customary to dismiss this fraction summarily either as an artefact due to immediate hydrolysis or as of no physiological importance. Following the development of new methods of analysis of N.E.F.A. in plasma,[1 2] however, it was soon found that the level of plasma-N.E.F.A. was not constant, but was readily reduced by insulin or by oral glucose and increased by adrenaline.[1 2] Unlike other lipid components of the blood it is relatively little affected by a fatty meal. The usual concentration of N.E.F.A. in plasma is between 0·5 and 1·0 m-mole per litre. A blood-sugar of 100 mg. per 100 ml. equals 5·5 m-mole per litre; so the molecular concentration of N.E.F.A. in plasma is usually some 5–10 times less than that of glucose. DOLE,[3] however, has calculated that, as the rate of turnover of N.E.F.A. in the blood is some 40 times greater than that of glucose, and as a molecule of N.E.F.A. provides on oxidation more than three times as much energy as a molecule of glucose, N.E.F.A. could easily supply the necessary fuel for muscular exercise, despite its low level in the plasma.

The fuel for the body is, of course, provided by the food, and in most diets 80–90% of the calories come from fat and carbohydrate. As long ago as 1866 PETTENKOFER and VOIT [4] showed that mechanical work did not increase protein metabolism; and this has since been confirmed experimentally. Alcohol can contribute significantly to the calories needed for the basal metabolism; but there is now good evidence, mostly supplied by French workers,[5] that it is not utilised by working muscles. In 1907 the classical work of FLETCHER and HOPKINS [6] revealed the relation of lactic acid to muscular activity, and this drew attention to the importance of carbohydrate in muscle. Subsequently MEYERHOF, A. V. HILL, and others in experiments on isolated muscle preparations showed the close relation of carbohydrate breakdown and lactic-acid formation with the development of muscle tension and the liberation of heat. HILL's [7] essay on Lactic Acid as the Keystone of Muscular Activity helped to lead to the idea that carbohydrate was the sole fuel of muscle. A popular view of physiologists was: "Fats must often be utilised for the carrying out of muscular work. For this to take place, it is probable however that they are first converted into carbohydrate and stored in the muscles as glycogen". [8] Carbohydrates were thus accredited as "the prime fuel" of muscle. On the other hand most biochemists have been sceptical as to whether fat is ever normally converted to carbohydrate in the body. In this they have been supported by RAPPORT,[9] who showed how unsatisfactory was all the evidence in favour of the formation of carbohydrate from fat in the body. In their textbooks biochemists often omit any reference to the fuel of muscle; but at one time many would have agreed with the concept, succinctly stated by PETERS and VAN SLYKE,[10] that fat is carried from the adipose tissues to

10. Luhby, A. L. *ibid.* p. 617.
11. Broquist, H., Luhby, A. L. *Proc. Soc. exp. Biol., N.Y.* 1959, **100**, 349.
12. Schulman, I. *J. Pediat.* 1959, **54**, 663.
13. Pierce, M. I. *ibid.* p. 691.

1. Dole, V. P. *J. clin. Invest.* 1956, **35**, 150.
2. Gordon, R. S., Cherkes, A. *ibid.* p. 206.
3. Dole, V. P. *in* Chemistry of Lipids as Related to Atherosclerosis (edited by Irvine H. Page); p. 194. Springfield, Ill., 1958.
4. Pettenkofer, M., Voit, E. *Z. Biol.* 1866, **2**, 537.
5. Le Breton, E., Tremolieres, J. *Proc. Nutr. Soc.* 1955, **14**, 93.
6. Fletcher, W. M., Hopkins, F. G. *J. Physiol.* 1907, **35**, 247.
7. Hill, A. V. *in* Certain Aspects of Biochemistry; p. 253. London, 1926.
8. Evans, C. L. *in* Principles of Human Physiology; p. 814. London, 1952.
9. Rapport, D. *Physiol. Rev.* 1930, **10**, 349.
10. Peters, J. P., Van Slyke, D. D. Quantitative Clinical Chemistry; vol. 1, p. 46. London, 1946.

the liver and there converted into ketone bodies: " to meet the demand for fat to furnish energy the liver pours ketones in the blood ".

Modern ideas stem largely from the experiments of STETTEN and BOXER.[11] In 1944, with the aid of deuterium, they showed that in rats on a high-carbohydrate diet only about 3% of the dietary glucose was handled as glycogen and at least 10 times as much was used to synthesise fatty acids as to synthesise glycogen. WERTHEIMER and SHAPIRO [12] have been pioneers in demonstrating that adipose tissue is not simply a stable store of fat, but an actively metabolising tissue capable of converting carbohydrate into fat and with a rapid rate of turnover of its chemical constituents. The opinion is now rapidly gaining ground that the major portion of the dietary carbohydrate is converted immediately to fat in the adipose tissues. During muscular exercise it is mobilised directly as N.E.F.A., which is carried direct to the working muscles. During transit in the blood N.E.F.A. is loosely bound to serum-albumin. Thus, fat rather than carbohydrate now seems to be the " prime fuel " of muscle. According to this view, the liver is less important in metabolism than has hitherto been supposed.

The classical work on carbohydrate is undoubtedly correct so far as the immediate source of fuel for a sudden burst of hard exercise is concerned: glycogen is the one fuel immediately available in muscle, and its breakdown to lactic acid certainly provides the energy for any burst of activity. But this mechanism is probably responsible for no more than a small fraction of the energy utilised in long-continued muscular work. BING et al.[13] have shown that heart-muscle can extract from the blood enough fat to account for 70% of the oxygen uptake. CARLSON and PERNOW [14] have carried out observations in man in which they catheterised both femoral veins and the subjects then exercised one leg only on a bicycle ergometer. At all levels of exercise the plasma from the femoral vein in the exercising leg contained less N.E.F.A. than that from the vein in the resting leg. These experiments thus provide direct support for the view that N.E.F.A. is directly utilised by active muscles.

If these newer views are even partly correct, then the mechanisms for mobilising N.E.F.A. from the adipose tissue are obviously of interest. Here growth hormone may be important. In the growing animal this hormone accelerates growth mainly by mobilising fat and so sparing protein and other nutrients for tissue synthesis. Experience with the new preparations of human growth hormone [15] indicates that in man this hormone immediately causes a sharp rise in the plasma-N.E.F.A. level. In the adult, growth hormone may well have a fundamental role in the mobilisation of fat as a fuel for muscular exercise. Further knowledge of how growth hormone and other possible fat-mobilising factors, such as that described by CHALMERS, KEKWICK, and PAWAN,[16] may lead to better understanding of the chemical pathology of some types of obesity.

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Tumour Viruses

THE Society for General Microbiology has held two symposia on virus multiplication. The first was in 1952, when the burning question was whether viruses behaved like bacteria and multiplied by binary fission or whether they were assembled in the cell from subunits. The second was held last April.[1] In the interval the primary role of the nucleic-acid component of viruses—either desoxyribosenucleic acid or ribonucleic acid—had been established for at least one representative of bacterial, plant, and animal viruses. The genetic information is contained in the nucleic acid; and on entry into the cell, where it is freed from the protein part of the virus, it becomes incorporated in, or to a greater or lesser extent takes over, the genetic system of the host cell. In this way the host cell is diverted more or less completely from producing copies of itself to producing new virus particles.

The sphere in which the technical and theoretical advances in virology may have their greatest impact is the study of tumours. At the symposium H. RUBIN discussed information about the virus of Rous sarcoma derived from the application of quantitative tissue-culture techniques. One factor against ready acceptance of the virus theory of the ætiology of cancer has been that after tumour-virus infection the host cell is not destroyed but is altered so that it becomes malignant—a property transmitted to its progeny. The difficulty arises because the cell is permanently altered although the continued presence of the virus is often difficult or impossible to detect. This could be explained on the basis of a temperate—that is to say, modified or limited — virus infection, on the analogy of temperate phage giving a lysogenic but virtually permanently infected culture. Technical advances are enabling a direct experimental attack to be made on these problems. TEMIN and RUBIN [2] have described a method of assaying Rous-sarcoma virus in chick-embryo cells in vitro. When a thin layer of chick-embryo cells is infected with Rous-sarcoma virus and overlaid with nutrient agar, colonies of altered cells can be readily counted. The numbers of these colonies are proportional to the concentration of virus, up to the point where 10% of the cells are infected. Apparently the cells are in a physiological state receptive of infection for only a short period. Infected cells are not killed, but continue to multiply and produce virus indefinitely. The yield of virus from a cell population is very low—about 1 infectious unit per cell per 1–10 hours. Such a low yield of virus is reminiscent of the behaviour of a lysogenic culture of bacteria. In a lysogenic bacterial culture a few cells release a large amount of virus and are killed in the process. Certain treatments, such as ultraviolet light, will induce phage formation by all the cells in a lysogenic culture with mass lysis and production of a large amount of bacteriophage. It is known that lysogeny may confer on the bacterial cell new properties which persist as long as the virus infection persists—for

1. Virus Growth and Variation. Edited by A. ISAACS and B. W. LACEY. London: Cambridge University Press, 1959. Pp. 272. 35*s*.
2. Temin, H. M., Rubin, H. *Virology*, 1958, **6**, 669.

example, toxin production by *Corynebacterium diphtheriæ*.[3] The hypothesis that tumour viruses behave like temperate phage is therefore very attractive. It appears, however, that all cells infected with Rous-sarcoma virus release virus and that such virus release does not kill the cell; isolated chick cells have been observed to divide after releasing virus into the surrounding medium. Pure clones of Rous-sarcoma cells grown in the presence of Rous-sarcoma-virus antiserum still produce virus; so reinfection of cells via the fluid phase of the medium does not account for the persistence of Rous-sarcoma virus. There must accordingly be some exact mechanism for distributing virus to daughter cells at division. Virulent and temperate phages have been found to be equally sensitive to X-irradiation, but temperate phages are much less sensitive to ultraviolet light. Comparison of Rous-sarcoma with Newcastle-disease virus showed that they were about equally sensitive to X rays but that Rous-sarcoma virus was 10 times less sensitive to ultraviolet light. Rous-sarcoma virus therefore in this respect closely resembles temperate phage. X-irradiation of cells with a dose preventing division destroys their ability to propagate Rous-sarcoma virus, whereas similar treatment leaves unimpaired the capacity to support Newcastle-disease virus. Virus-infected cells do not, however, cease to produce virus unless the dose of X rays greatly exceeds the amount inhibiting cell division and the capacity to become infected with Rous-sarcoma virus.

Quantitative studies of the behaviour of Rous-sarcoma virus have also resolved conflict about the detection of normal chicken antigens in this virus. The virus is not neutralised by antisera to normal chick tissues, but the multiplication of Rous-sarcoma cells is. RUBIN also suggests that the interesting observation of HARRIS and SIMONS [4] that young turkeys can be rendered susceptible to Rous-sarcoma virus by pretreatment with normal chick red blood-cells may be interpreted by analogy with observations made on temperate phage infection of the salmonella group of bacteria. UETAKE et al.[5] found that new somatic antigens appeared in salmonella species infected with temperate phage. Similarly infection with Rous-sarcoma virus might lead to turkey cells producing chick antigens. In normal turkeys these antigens would yield antibodies destroying the tumour. On the other hand, turkeys with acquired immunological tolerance to chick antigens would fail to produce antibodies and thus be susceptible to infection with Rous-sarcoma virus.

The work with Rous-sarcoma virus summarised and mainly done by RUBIN suggests that this virus may resemble a temperate bacteriophage in being closely integrated with the host cell. Some tumour viruses, on the other hand, appear to be virulent cytocidal viruses for cells in vitro—for example, the Stewart-Eddy polyoma virus [6] destroys monkey-kidney cells in vitro. The fact that neutralising antibodies are produced against tumour viruses, and that some of these viruses are cytocidal for cells in vitro giving high yields of virus, opens the possibility of preparing a vaccine against specific ætiological agents of cancer. Already FRIEND[7] has reported that in mice the virus leukæmia discovered by her can be prevented by immunisation with formaldehyde-inactivated virus, and the leucosis complex of fowls, extensively studied by BURMESTER [8] and by others, can probably also be prevented by vaccine. The application of this work to human cancer will depend on the discovery of a virus cause for a human malignant tumour; the search will be greatly aided by recent technical advances.[9] Although proving an ætiological association is likely to be a formidable task, it seems most unlikely that man alone is exempt from tumour-virus infections.

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9. See *Lancet*, Aug. 1, 1959, p. 76.

Annotations

SCIENCE, PUBLIC, AND PROFESSION

NOT long ago someone analysed the attitude of American schoolchildren to the scientist. On the negative side of the image some of the worst faults attributed were that he had lost the public's confidence, neglected his family, and lived in a cold-water flat. English readers who would like to confirm these views should be in York this week for the annual meeting of the British Association for the Advancement of Science. Nowadays this lusty centenarian is concerned not so much with the advancement as with the dissemination of scientific knowledge among the general public, and Sir James Gray's presidential address (like those of his forerunners) is largely devoted to this problem. The most surprising thing is that it should be necessary at all. When *The Origin of Species* appeared, most educated men seem to have understood it well enough to know that something important had happened, and so entirely have the lessons of this book been incorporated in our thought that it is hard to imagine what would happen if it were published for the first time tomorrow. In this century the scientist and the reading public have, in fact, diverged. That Jeans' *The Stars in their Courses* was a best-seller suggests that the blame does not lie entirely with a lazy-minded reading public. No doubt our ignorance of mathematics has played a part, but (*pace* Bronowski) translation into English is sometimes possible. The exponents of the physical sciences may well say that if they wrote no-one would read; but far too few have put this to the test. The biologists have done better. Such scholars as Sir Julian Huxley, J. B. S. Haldane, and Sir James Gray himself have all played a part in telling Tom, Dick, and Harry what they and their colleagues are doing; and it may be pertinent that all three have seen more of the world than can be seen from a laboratory window. It may be, too, that the biological sciences are better understood because most of us grow lettuces or keep a dog, whereas a Wimshurst machine is a rare ornament in any drawing-room.

It is equally unfortunate that the public seldom realises what it loses by the divorce of scientific understanding (except in its most banal applications) from common life. Chemistry is no less and no more interesting than history or any other subject which can stir the imagination. So complete is the divorce that, as Sir James says, the physicists have actually frightened the public—much as an African secret society terrifies those who have not

been initiated. Nearer home, a public much concerned with health and disease still imagines that the smell of sewage is unhealthy as well as unpleasant. From all this ignorance springs antipathy, and from antipathy a conscious and noisy antiscience—horoscopes, herbalists, and muck-and-magic farming.

The popular remedy for this lack of communication is more science teaching in schools; and, as this could affect the career of every medical student, it is of special concern to our profession. Teaching science well is difficult, and good teachers are rare—though not so rare as they were. The scientific curriculum contains a lot of facts (which are easy to teach) and some general ideas (which are not): whereas the boy studying " the classics " may by the age of 16 be seeing in a dim way what it is all about, his scientific coeval may merely be trying to memorise information. Since almost all educationists agree that their main object is to teach children how to learn and how to think, few really favour their early introduction to vocational as opposed to educational courses, and many, if not most, would rightly prefer boys and girls taking medicine to postpone for a year or two their present early start on preparation for the 1st M.B. Is this to be one more of the valuable things which we in this country are for some reason supposed to be no longer able to afford? It is really impossible to believe that anyone who has limited his reading to scientific cram-books since the age of 16 is the best candidate for a humane profession.

EPIDEMIC PRIMARY INTERSTITIAL MYOCARDITIS IN CHILDHOOD

DURING the past sixty years, acute interstitial myocarditis has become a well-recognised clinical and pathological entity. Fiedler [1] described the first adult case in 1899, and Zuppinger [2] recorded a similar condition in a child; since then many cases have been seen in all parts of the world. Between 1937 and 1944 there were 140 cases in the Munich area [3] in children between the ages of one month and two years. Over 75% of these were under eight months old and only 1 child survived. The epidemic was protracted, with 8–25 cases yearly in localised areas in the city. During this period there was no increased incidence of diseases known to be associated with myocarditis. Coxsackie virus was responsible for outbreaks among newborn babies in South Africa and Southern Rhodesia [4 5] at times when Bornholm disease was prevalent, and in Amsterdam [6] during a period of " summer grippe ". In Athens [7] in 1956 there was a considerable increase in the number of cases of interstitial myocarditis when 6 out of 8 cases were fatal.

The most recent epidemic has been reported from Israel, where it was confined to Haifa and involved 57 children, most of whom were aged between six and eighteen months.[8–10] Unlike most previously reported epidemics, it involved no infants under six months of age. Sporadic cases had occurred in previous years and there was a sharp rise of incidence during 1956, reaching a peak in February, 1957. No other epidemic conditions existed at the time, and no parents or siblings of affected cases suffered from any other disease. The clinical features were essentially those of acute cardiac failure, which failed to respond to a number of drugs and which was fatal in 50 children. Munk and Lederer [9] have described the radiological appearances, in which the predominant feature was general cardiac enlargement progressing from slight dilatation, when the shape of the heart was well preserved, to extreme enlargement with a globular cardiac shadow. All patients had passive pulmonary congestion and a few had pleural effusions. The histopathological evidence of severe interstitial infiltration of the myocardium by lymphocyte-like cells was sometimes accompanied by diffuse interstitial pneumonia or by areas of subendocardial fibrosis. A number of cases showed interstitial inflammatory infiltration in other parts of the body—particularly the liver, diaphragm, psoas muscle, and pericardium. On p. 263 of this issue Dr. Heichmann and Dr. Bassan record the electrocardiographic findings in 21 cases and point out that in no case was a defect of the conduction mechanism seen; this was confirmed by the failure to find pathological changes in the conducting tissue in spite of the severe abnormalities in the rest of the myocardium. Mice inoculated with postmortem material failed to develop disease after several passages, although an unidentified virus from the heart of a fatal case was grown on monkey-kidney tissue culture.[8] While it has been shown that Coxsackie virus can cause myocarditis, particularly in small babies, the ætiology of most cases remains obscure. Schmidt [10] has isolated an " encephalomyocarditis virus " from chimpanzees dying with interstitial myocarditis, but this virus has been recovered only from human patients with cerebrospinal conditions. The studies in the Haifa epidemic exclude the Coxsackie virus as well as the encephalomyocarditis virus or similar viruses as ætiological agents. Thus although it appears that acute interstitial myocarditis, whether sporadic or epidemic, is viral in origin, it is likely that several viruses may be responsible.

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THE CHOICE OF DIURETIC

FORTY years ago in a Vienna hospital, Vogl made a chance observation which opened a new era of diuretic therapy.[1] While treating a syphilitic patient with an organic mercurial, he noted that it effected prompt diuresis. This led to the development of mersalyl and similar compounds which are universally used in the management of œdematous states. Organic mercurials are cheap and their toxicity is low. Their chief disadvantage is that they must be administered parenterally. The mercurials now have competitors in the oral chlorothiazides, and in the foreseeable future these will be joined by the spirolactones and others with distinctive modes of action.

" Diuresis and diuretics " was the topical theme of a conference held in June at Herrenchiemsee, under the chairmanship of Prof. H. Schwiegk, of Munich. Reviewing the physiology and pharmacology, Dr. R. F. Pitts (New York) suggested that the chlorothiazides and organic mercurials interfered with the energy of the ion-pump in the kidney, perhaps by blocking different enzyme systems. Dr. R. Hess (Basle) has studied the histochemistry of hydrolytic and oxidative enzymes in the nephron of the rat kidney in health and disease, in an effort to

1. Vogl, A. Diuretic Therapy; p. 104. Baltimore, 1953.

detect the site and mode of action of diuretics. Alterations in mitochondrial activity in certain parts of the proximal and distal tubules were greater following organomercurials than other diuretics. In studies with Dr. E. M. Darmady, Dr. R. Gaunt (Summit, N.J.) demonstrated that labelled hydrochlorothiazide collected in the distal parts of the proximal convoluted tubules. He found that hydrochlorothiazide caused much greater sodium, chloride, potassium, and water excretion than chlorothiazide, ranging from twenty times greater in the rat to five or ten times greater in the dog. Its carbonic-anhydrase inhibition was a tenth that of chlorothiazide. It antagonised the sodium-retaining effect of aldosterone and of deoxycortone acetate, enhanced the natriuretic and diuretic effects of prednisolone, and also enhanced the diuretic effect of alcohol as an antidiuretic-hormone inhibitor. In man, hydrochlorothiazide is considered to be about ten times more potent than chlorothiazide.[2 3] A similar response can be expected from a daily dose of 1 g. chlorothiazide or 100 mg. hydrochlorothiazide; the latter carries no particular advantage for the patient except that he swallows a slightly smaller pill.

Dr. C. K. Friedberg (New York) had analysed the value of diuretics in 1000 personally studied cases of congestive cardiac failure. The diuretic response was excellent or good in two-thirds, poor in a quarter, and only slight in the remainder. The poorest response was often related to a complicating factor such as subacute bacterial endocarditis, tricuspid regurgitation, or respiratory tract infection. He continues to advocate the use of mercurial diuretics by injection, despite the ease of administration of the oral chlorothiazides. He still believes in the value of a strict low-sodium diet and feels that patients taking oral chlorothiazide might become careless of their diet, much like a diabetic receiving insulin. He administers chlorothiazides mainly as interval therapy between courses of mercurial diuretics and also when long-term diuretic therapy is indicated.

In contrast, Dr. R. Richterich (Basle) has abandoned mercurial diuretics in favour of small doses of the chlorothiazides. He is finding that satisfactory diuresis can be achieved by these oral drugs without restricting salt and water intake. Likewise in Vienna, Dr. F. Wewalka has abandoned mercurial diuretics in favour of chlorothiazides because the latter provide a smoother controllable diuresis, whereas mercurial diuretics often provoke massive diuresis, exhausting to the patient and sometimes followed by an undesirable rebound phase of water retention. Dr. F. Gross (Basle) pointed out that during this rebound phase there was an increase in aldosterone secretion, which would be accompanied by sodium retention likely to negate the results of the previous diuresis. Possibly chlorothiazide may usurp irksome dietary restrictions in mild and transient states of salt and water retention, but no good argument has yet been put forward for abandoning dietary sodium restriction in congestive cardiac failure or portal cirrhosis with ascites; in these conditions all too often the patient responds well to a rigid diet in hospital, only to relapse when he returns home.

Dr. Friedberg drew attention to certain undesirable effects of the long-term use of the chlorothiazides—namely, cardiac arrhythmias, hyperuricæmia leading to attacks of gout, and increased urinary potassium excretion; potassium excretion was increased still further if the patient was also receiving corticosteroids. Dr. Sheila Sherlock (London) also stressed the danger of increased urinary potassium excretion following administration of the chlorothiazides in the management of decompensated liver disease. The chlorothiazides may cause clinical and electroencephalographic changes of impending hepatic coma; but these changes can be corrected by adequate potassium supplements.[3–5] It is, therefore, essential to give potassium with the chlorothiazides whenever these are administered for long periods, particularly in liver disease.

As regards the management of ascites, Dr. Sherlock referred to the organic mercurials and the chlorothiazides and also to intravenous infusions of albumin. Repeated doses of 100 g. of albumin over long periods sometimes produce satisfactory diuresis, but albumin is at present prohibitively expensive and virtually unobtainable.

The effect of aldosterone on electrolyte metabolism is twenty to thirty times greater than that of deoxycorticone. All the evidence suggests that aldosterone plays an important part in maintaining fluid and electrolyte homœostasis. A low-sodium or high-potassium diet leads to increased aldosterone secretion. It promotes sodium retention and potassium excretion, and a close inverse relationship exists between sodium and aldosterone excretion in œdematous patients.[6 7] It is not surprising, therefore, that the aldosterone-antagonising compounds—the steroidal spirolactones—should be tried in patients with œdema. The earlier compounds were administered parenterally, but Dr. W. Hollander (Boston) and Dr. Sherlock reported experience with a recent one—'SC9420', 'Spironolactone'—which can be given by mouth. It appears to be an effective diuretic, promoting sodium excretion with no accompanying potassium excretion. Thus far its scarcity precludes its free use, but it is clearly a promising addition. Theoretically it should cause a positive potassium balance. Thus, chlorothiazide combined with spirolactone would seem an attractive combination for the management of obstinate œdema. Dr. Hollander has noted that the combined use of chlorothiazide and a spirolactone potentiates not only the diuretic effect but also the antihypertensive effect.

Dr. V. Friedberg (Mainz) attributes the poor diuretic response to chlorothiazide in toxæmia of pregnancy to the low plasma-volume. When this is corrected by intravenous albumin, chlorothiazide causes satisfactory diuresis. He also believed that a poor antihypertensive effect of chlorothiazide in pregnancy toxæmia was due to hypovolæmia. Urinary aldosterone levels, although raised in pregnancy, were found to be lower in toxæmic patients than levels observed in normal cyesis at the same stage. This apparent paradox of lower aldosterone excretion in the presence of sodium retention may be related to the low progesterone levels in toxæmia of pregnancy. Progesterone appears to exert its natriuretic effect only in the presence of adequate aldosterone excretion.

The proceedings of this conference are to be published by Springer-Verlag, Heidelberg.

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DEMETHYLCHLORTETRACYCLINE

COMPARING it with corresponding doses of tetracycline, Kunin and Finland [1] found that, given to normal persons by mouth, the new tetracycline antibiotic, demethylchlortetracycline, produced higher and better-sustained levels of antibacterial activity in the serum. On the other hand, Sweeney et al.,[2] giving 250 mg. of each of the antibiotics, reported that demethylchlortetracycline was 25% less active than chlortetracycline—though in a turbimetric test its activity against a strain of *Staphylococcus aureus* was three times as high as that of tetracycline or oxytetracycline. This apparent contradiction evidently arises from the two different ways of expressing antibacterial activity of the serum—in relation to the actual amount of each antibiotic ingested or in relation to its tetracycline equivalent.

Hirsch and Finland [3] have now compared the antibacterial activity acquired by the serum of the same normal subjects after ingestion of equivalent doses of demethylchlortetracycline, oxytetracycline, and chlortetracycline: each antibiotic was given in a dose yielding 250 mg. of the respective hydrochloride. Briefly, the results showed that demethylchlortetracycline was absorbed as well as, or better than, equal doses of either chlortetracycline or oxytetracycline in combination with glucosamine. The new antibiotic also produced more antibacterial activity in the serum than the other two analogues when they were compared in terms of the concentration of antibiotic expressed as activity of any one of the analogues. The antibacterial activity of the serum persisted 24–48 hours longer than with chlortetracycline or oxytetracycline. We may conclude that this establishes the need to use the same standard of reference in comparing different but related drugs. To make a valid comparison of the probable therapeutic usefulness of the drugs, it is their relative antibacterial activity that must be measured.

On this basis demethylchlortetracycline emerges from the present investigations as likely to be the best of the tetracyclines so far available. The final test of all these matters, of course, is the result of a properly controlled and critically analysed clinical trial.

ÆTIOLOGY OF PICA

PICA, or perverted appetite, is prevalent in all parts of the world, especially among populations suffering from chronic malnutrition, and it is commonest in children and pregnant women.[4] In this country it is rare for children to be brought to the doctor because of pica; but maybe more children than we realise exhibit this odd behaviour, for, unless the child comes to grief as a result of his indulgence, parents seem loth to mention it to the doctor. Lead-poisoning as a result of eating flakes of paint is a well-recognised hazard of pica in civilised countries and is the most dangerous. Experience has shown that parents very rarely admit that the child has been chewing paintwork until they are questioned further after the diagnosis has been confirmed.

Pica has been ascribed to mental deficiency, behaviour disorders, worm infestations, malnutrition, pregnancy, and anæmia. Hancock [5] attributed it to " paucity of good blood and lack of proper nutrition ". Gould [6] reported a case cured by iron therapy. The explorer, David Livingstone, according to Waller,[7] commented on the habit of earth and clay eating amongst African tribes in Zanzibar and said that " it was the cause of bloodlessness among them ". Clay eating appears to be extremely common in Africans and some tribes in Brazil. In Africa it is often associated with magical beliefs and is not the kind of subject to be discussed with a white man.[8] Cooper [4] described a Negro family in Baltimore three female members of which regularly consumed refined clay delivered in a sack to their house by the local brickyard. Many clay eaters are highly selective and take great trouble to find the most palatable varieties in their area. There is some evidence that a few types of clay may contain enough sodium, potassium, and iron to give them some nutritive value. Recently, Lanzkowsky,[8] working in Cape Town, noticed that severe anæmia in children appeared to be associated with pica. He treated the anæmia with injections of iron-dextran compound and was able to record rapid disappearance of both pica and anæmia. There were 12 children in his series, 10 Cape coloured and 2 white, whose ages ranged from $1^1/_2$ to $6^1/_2$ years; they had all been in the habit of eating large amounts of sand, pebbles, or brick fragments. Many showed these foreign bodies in plain X-ray films of the abdomen. The general nutrition of these children was good and their parents were not especially poor. The mean hæmoglobin level of the pica group was 7·9 g. per 100 ml., with a mean corpuscular-hæmoglobin concentration of 27·5%, compared with a control group of anæmic children without pica in whom the mean hæmoglobin level was 10·5. Other investigations in the pica group showed a high incidence of intestinal worm infestation, but no evidence of mental retardation, severe behaviour disturbance, or low birthweight. Lanzkowsky decided to treat all the pica children with parenteral iron to ensure absorption of iron. All symptoms of pica disappeared by the end of two weeks, and follow-up disclosed no relapses. It is interesting to speculate on which is the primary disorder, the anæmia or the pica; for it is clear that prolonged pica leads to anæmia, yet it is odd that sudden increase of the iron stores of the body should lead to abrupt cessation of pica. Iron-deficiency is probably the most widespread mineral deficiency in the human child and Lanzkowsky suggests that by a primitive instinct the child seeks to supplement its iron stores by eating earth and clay, which sometimes contain some elemental iron. There is experimental evidence for this hypothesis in animals, both from laboratory and field. Osteomalacic cattle have been observed to eat bones offered to them or left lying in the fields but ceased to do so when given a phosphorus-rich diet. Children with parathyroid deficiency have been known to crave plaster and chalk.

It seems that Kanner's belief [9] that pica is a symptom of mental retardation may have to be revised; perhaps his series of retarded children with pica also had anæmia. There is clearly scope for further investigation—for instance, a study of serum-iron levels before and after treatment might yield interesting data. Pædiatricians might ask some searching questions about diet, normal and otherwise, when they encounter young children with severe iron-deficiency anæmia, for there may be more to it than meets the eye.

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Special Articles

A DISTRICT PSYCHIATRIC SERVICE

THE BOLTON PATTERN

J. T. LEYBERG
M.D. Polish Sch. Med., Edin., D.P.M.
CONSULTANT PSYCHIATRIST, BOLTON GROUP OF HOSPITALS

SINCE the introduction of the National Health Service there have been interesting developments in the psychiatric services, and it is hoped that the Mental Health Act will lead to further progress. These changes are meant to provide better facilities for early treatment, allowing the patient to be treated while remaining in the community, and to bring psychiatry closer to general medicine, thus overcoming the traditional isolation of mental hospitals.

Nowadays the pattern of psychiatric services is becoming more flexible, attempting to meet local needs. The number of outpatient clinics served by mental-hospital psychiatrists doubled between 1954 and 1956 (Godber 1958), and cooperation between the hospital and the local authority has been fostered (Macmillan 1958, Pool 1958). In some parts of the country, separate day hospitals have been set up, and some mental hospitals have started accepting day patients. The Worthing service (Carse et al. 1958) has admirably combined treatment in the community with effective screening and has reduced the number of mental hospital beds needed in its area. Physical methods of treatment are being used successfully in outpatient clinics (Cook 1958, Harper 1959).

A rather different pattern has been gradually emerging in the Manchester region and has been followed in the Bolton district since 1953.

The Service and its Patients

Our aim is to provide a service for a highly industrialised urban area of a quarter of a million people, most of whom live within 7 miles of the general hospital which houses our psychiatric unit. The unit serves the borough of Bolton (population 165,000) and parts of the Lancashire County (population 85,000). It deals only with adults.

It has been the policy of the Manchester Regional Hospital Board, which took over large, overcrowded mental hospitals, often caring for over 3000 patients, to develop their peripheral psychiatric units in general hospitals by gradually upgrading former poor-law institutions. Units of this kind, integrated into the framework of general hospitals, have now enough staff and equipment to offer inpatient and outpatient treatment. They have reduced considerably the demand on regional mental hospitals.

The Bolton service, staffed by a part-time consultant, a senior registrar, and a resident senior house-officer, is based on Townleys psychiatric unit of 164 " designated " beds in the grounds of a large general hospital. In addition, 3 beds for each sex are available in the medical wards of the hospital. The medical staff has no commitments in any mental hospital.

Inpatients

The unit admits all types of psychiatric patients after careful screening through outpatient clinics, domiciliary visiting, or on the request of the duly authorised officers. The number of admissions rose from 231 in 1950 to 335 in 1958, and the proportion of voluntary admissions from 2% to 91%. The table shows the diagnostic classification of admissions in 1958.

DIAGNOSTIC CLASSIFICATION OF 1958 ADMISSIONS

Depressions (including involutional depressions)	108
Manic states	14
Schizophrenias	59
Schizo-affective disorders	8
Paranoid states	12
Puerperal psychoses	8
Confusional states (postoperative and others)	7
Senile dementias	46
Arteriosclerotic and pre-senile dementias	26
Epileptic psychoses	6
Alcoholic disorders	8
Organic dementias (including G.P.I., cerebral tumours, Parkinson's disease)	10
Psychoneuroses	12
Psychopathic personalities	11
Total	335

Readmissions included in total admissions	45	(13·4%)
Patients from outside Bolton and district	28	
Patients from the Bolton and County area	307	

A large number of elderly patients with organic disorders had to be accommodated, many of them being transferred from other departments of the hospital.

The unit is run on the open-door principle, as a therapeutic community, with frequent visiting, town parole, weekend leaves, and close contact with the patients' relatives. The pathological laboratory, X-ray department, and consultative services of the hospital allow each case to be fully investigated. The comparatively small number of patients, who remain under the care of the same psychiatrist throughout their illness, favour a satisfactory doctor/patient relationship. All recognised forms of physical treatment are used. A few patients who need specialised treatment, such as insulin coma therapy or prefrontal leucotomy, are referred to the nearby regional mental hospital. Despite the open doors, it was found that few patients could not be treated within the grounds of a general hospital, and for many even of the more disturbed patients this environment proved helpful. The number considered unsuitable for treatment in a general hospital did not exceed 5 in any year.

Day Patients

Since 1953 only patients who could not remain at home have been admitted to the psychiatric unit. Up to 25 patients of each sex attend as day patients and during last year 156 new day patients were treated. They have their own diningroom, but they share the occupational therapy department with selected inpatients. They receive treatment in one of the hospital wards. We use the local health authority ambulance services, and if necessary patients are brought by ambulance in the morning and returned home in the late afternoon.

The following types of patient attend daily:

1. Cases of depression where the home background is satisfactory but the severity of the illness makes it inadvisable to carry out treatment in the outpatient clinic.

2. Patients who have completed inpatient treatment but whose recovery has not been long enough to exclude an early relapse.

3. Chronic schizophrenics who need occasional maintenance treatment and would otherwise have to stay in hospital. Some of our day patients have spent several years in mental hospitals, but with day treatment they are able to live at home.

4. A small group of senile dements who, because of social needs, have to be cared for during the day while their families are at work.

The advantages of day-hospital treatment are well recognised (Bierer 1951, Harris 1957), but it can sometimes become difficult to discharge the patients who may develop overdependency on the hospital or the group. This is not uncommon among those who live alone or are unemployed.

Outpatients

Outpatient clinics are held in the two main hospitals in the group: diagnostic (twice weekly), E.C.T. (twice weekly), aftercare and follow-up (once weekly), psychotherapy (once weekly). In 1957, 426 new and 2951 old patients were treated. E.C.T. was given to 128 outpatients, the average number of treatments per patient being 4·8. The type of patient does not differ essentially from the average patient attending a psychiatric clinic in a provincial hospital. The clinics, as one would expect, carry a heavy load of chronic psychoneurotics to whom they offer some supportive treatment. As in many other provincial centres, our psychotherapeutic facilities are totally inadequate, and owing to shortage of staff and time we have to concentrate on the few who are likely to respond to short-term psychotherapy.

Other Features

Consultations in General Wards

Besides the designated beds, 6 beds in medical wards are used for patients who need special investigations, for those with milder depressions, and for some psychoneurotics whom it is not desirable to admit to the psychiatric unit.

Consultations in general wards are often sought by other specialties and are interesting experience for the psychiatrist. In 1958, 173 patients were seen in the wards. All attempts at suicide are seen as soon as the patient is fit to be interviewed, and 94 of these patients were seen in medical, surgical, and casualty wards. Many would have otherwise drifted unnecessarily to mental wards. These consultations help other members of the medical and nursing staff to reorientate their attitudes towards patients with psychiatric disorders.

Domiciliary Service

Domiciliary visits are very often requested by general practitioners, particularly for patients who either cannot or refuse to attend the clinics, and in emergencies. By visiting the home, we try to screen as many patients as possible before admission to hospital; but we have not enough staff to provide a service as comprehensive as at Worthing. Mental-health officers continue to supervise the patients at home if necessary. The number of domiciliary visits made in 1958 was 188, and the patients were dealt with as follows:

Remained at home under the care of the practitioner	37 (20%)
Treatment continued in outpatient clinic..	68 (36%)
Admitted to hospital or treated in day hospital	83 (44%)

Liaison with Local Health Authority

We hold fortnightly meetings with mental-health officers when common problems are discussed, follow-up and aftercare arranged, and patients of some interest demonstrated. A course of lectures on clinical and social psychiatry was given to the mental-health officers at the start of the scheme. They undertake a considerable amount of social work, attend outpatient clinics, make field inquiries, and provide social histories. Close contact is maintained with the medical officers of health. All discharges and admissions from hospitals outside the psychiatric unit are notified to the psychiatrist, who is also kept informed of the waiting-lists and receives monthly and annual statistical analyses of psychiatric admissions and discharges from his area.

Psychiatric Social Club

The social club is run jointly with the local health authority, and meets weekly in one of their premises. It is supervised by a committee of ex-patients with the help of the mental-health workers. Its membership consists of some inpatients, who come from the hospital to the club, some outpatients and ex-patients. It aims at allowing members who share similar emotional experiences to grow into a group, it helps the socially isolated to form positive relationships, and provides some aftercare. One of the psychiatrists always attends the meetings. The club programme includes group discussions, lectures, films, panel games, and socials.

Effect on Admissions

In 1950 210 patients from the area were admitted to mental hospitals and 155 to the psychiatric unit. The comparable figures for 1958, when the service was in full swing, were 72 and 307.

The total number of admissions from the area remained about the same. (It is below the national average —1·5 per 1000 compared with 1·9.) As Parnell and Skottowe (1958) point out, the remarkable fall in admissions achieved in Worthing may be partly due to the high admission-rate there in 1956—4·1 per 1000. There was, however, a definite redistribution of our admissions. Whereas in 1950 nearly two-thirds of our patients were admitted to mental hospitals in 1958 the proportion had fallen to less than a fifth. The readmission-rate of 13·4% is also much lower than the national average of 44·3%, for every effort is made to treat a relapsing patient as an outpatient or day patient.

Discussion

Our results at Bolton support the view that a district-service saves beds. But to plan a service with this as its primary aim would be unwise, for there are many patients to whom outpatient and day-hospital treatment cannot be offered without serious risk or hardship to their families. With more people seeking treatment and an ageing population, the acute demand will continue until separate accommodation is provided for the aged.

Apart, however, from saving beds, a psychiatric service within the framework of a general hospital has many real clinical and social advantages, because it is accessible and readily accepted by the community, and it helps to break down the isolation and prejudice which still surrounds some mental hospitals. It brings the psychiatrist into closer contact with other specialties, with family doctors, and with the local public-health services. It relieves him of administrative preoccupations which are often unavoidable in a mental hospital. A district service of this type is practicable only in a densely populated district where travelling is easy and there is ready access to the hospital.

A psychiatric unit in a general hospital can never offer the best conditions for rehabilitation to chronic patients, particularly the female schizophrenics. As the number of chronic patients gradually increases—and 62% of our patients have been in hospital for over two years—a small unit may soon become unable to admit new cases. A good relation with the mental hospital is of paramount importance and a change of outlook is necessary. The mental hospital benefits by having to cope with fewer patients from the area and receives patients who have been better selected, but it is doubtful whether it will continue to receive patients " mostly with a good prognosis " (Carse et al. 1958); for many of these will be treated at home or in the general hospital.

A district service may soon become overburdened with responsibilities which could be carried by the local authority. The chronic psychotic who attends a day hospital, the relieved patient who has no family and

nowhere to live, the harmless senile dement—all these are soon thrust on the service.

Despite these drawbacks a district psychiatric service, working with a general hospital and the local health authority, allows many more patients to be treated in the community or in their local hospital, and in densely populated areas it should become the pattern for the future.

I wish to thank Dr. J. B. S. Mackay, deputy senior adminstrative medical officer of the Manchester Regional Hospital Board, for statistical figures. My thanks are also due to Dr. R. W. Elliott, lately medical officer of health for Bolton; to Dr. E. Taylor, divisional medical officer, Lancashire County; to Mr. D. Ernsting, hospital secretary; and to the mental health officers of the area for their cooperation in the development of this service. The opinions expressed in this paper are, of course, entirely my own.

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THE ADMINISTRATION OF DRUGS IN HOSPITALS

P. J. FOWLER
F.P.S.

FORMERLY GROUP PHARMACIST, SOUTHMEAD HOSPITAL, BRISTOL

THE administration of drugs in hospitals is becoming increasingly difficult. New drugs are being introduced so quickly that it is almost impossible for any member of the hospital staff to keep abreast of all new developments: the hospital pharmacist finds established methods of providing information about them inadequate; doctors cannot carry in their memory all details of drugs and dosage; and nurses, with many other duties, cannot be expected to have more than a superficial knowledge of all the new medicines they are using. These often appear under several different names.

THE MEDICINE LIST

For many decades ward sisters have ensured that patients received the drugs ordered for them by compiling a " medicine list ". This was satisfactory when fewer drugs were used: nurses could be expected to know a great deal about their action and side-effects; changes in treatment were infrequent; and making out new medicine lists was a simple task. The medicine list, however, has become totally inadequate. Patients today often receive four or five different preparations at the same time, changes in treatment are frequent, and the turnover is rapid. Drugs have, moreover, increased in potency: a single dose omitted or doubled can have serious results.

The advantages of the medicine list are as follows:

1. It indicates to the nurse which patients should receive medicine at what time.

2. It helps her to assemble the medicines for the round.

3. It supplies a list of patients in ward order.

The disadvantages can also be summarised:

1. Alteration can be made only by deleting an entry and adding the new treatment above it.

2. Movements of patients in the ward are difficult to record. This can result in errors from mistaken identification.

3. The task of making out new medicine lists has become very time-consuming. New lists tend to be made from old ones; and errors are thus perpetuated.

4. Two or three lists for various types of drugs are necessary on most wards.

5. Each ward sister has a slightly different way of making up the list; and this is confusing to the night staff.

On these grounds the medicine list can be condemned; and we must find a satisfactory substitute. The one suggested by the Aitken Committee—that " every medicine, whether or not it is a dangerous drug or Schedule-One poison, should be checked against the prescription, i.e., the treatment sheet at the bed-side, immediately before administration " [1]—would surely lead to even more errors than the medicine list. The interpretation of prescriptions is not always easy, even in the pharmacy; and to entrust this to any nurse each time she gives a dose is to court disaster.

The problem of interpretation of a badly written prescription is now being re-examined by pharmacists. Before the war, they could interpret a badly written prescription with a great degree of certainty because of the small number of drugs; but the position is quite different today. We have, for example, as many as fifty preparations beginning with " per " or " pen ", and pharmacists have to make more and more inquiries to ensure that the drug they are dispensing is the correct one. 80–90% of prescriptions in hospitals are written by house-

1. Control of Dangerous Drugs and Poisons in Hospitals. Report of Central Health Services Council: Joint Subcommittee on the control of Drugs and Poisons in Hospitals. See *Lancet*, 1958, i, 422

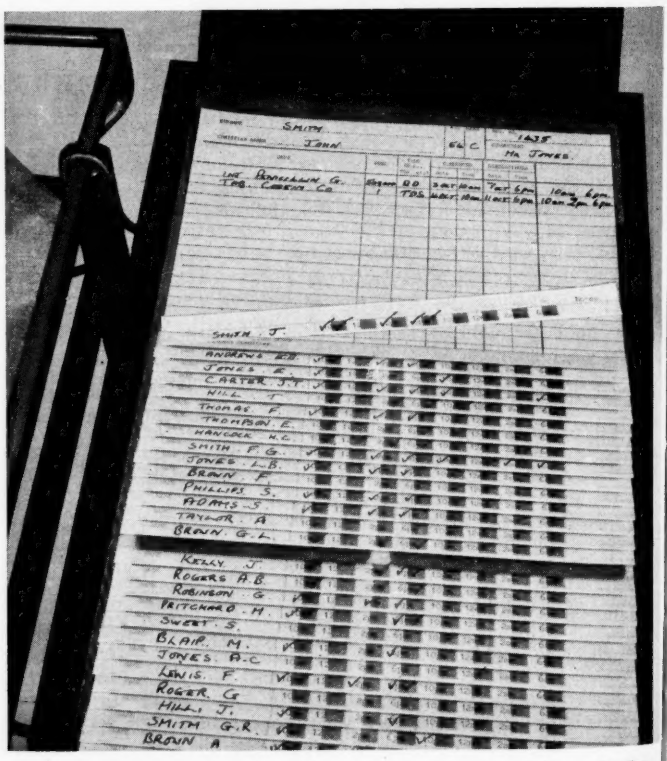


Fig. 1—The fold-flat file with the medicine sheets of patients arranged in ward order.

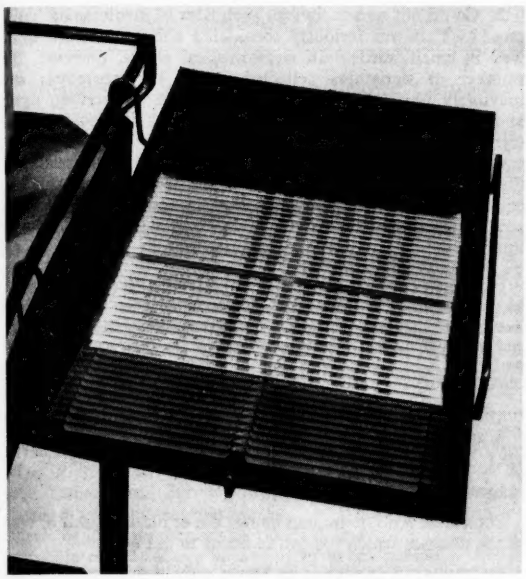


Fig. 2—The file attached to the medicine trolley.

officers who are writing their first prescriptions; and quite often they omit one or more essential facts. The pharmacist has to interpret such prescriptions once only, whereas the nurse must interpret them each time a dose is given.

After a prescription has been written on the patient's treatment sheet it is necessary for the sister to add on the medicine list further information: the number of days of treatment still to come, the times at which the doses shall be administered, and any additional warning arising from the ward round.

A NEW SCHEME

This problem has been studied for some years; and a scheme was devised to eliminate the drawbacks of the medicine list while exploiting more fully its potential advantages. It has the following main features:

1. A fold-flat file replaces the medicine list. Each patient has a sheet in this file, arranged in ward order (figs. 1 and 2). An indicator strip is attached to the bottom of every sheet: it is divided into eight squares, one for each ward round of the day and night. Each square is subdivided into a plain and shaded area for medicine-rounds and injection-rounds respectively (fig. 3).

2. The nurse does not have to rely on her own interpretation of the prescription. The sister has to make one—and only one—copy of the prescription, written in such a form that all nurses can interpret it without difficulty.

3. The sister records this interpretation of the prescription immediately after the ward round when she still has fresh knowledge of what was intended. The details are written on one line on the patient's sheet in the fold-flat file. This entry is never transcribed, except on the very rare occasion when the patient's sheet is filled completely—i.e., after thirty prescriptions.

4. The information given in the prescription is written in tabulated form so that sister can see that the full information is available to the nurses making the medicine round.

5. A rapid indicator helps nurses to assemble the required drugs on the trolley before starting the medicine round.

6. A precise statement of the length of treatment and the times at which doses should be administered are recorded by the sister.

7. When the treatment is changed the old entry is deleted by drawing a single line through it and the new prescription is recorded on the line below.

The nurse assembles the drugs required for each medicine round by consulting the indicator strips attached to the medicine sheet of each patient: a tick indicates when a patient is due for a dose of medicine or an injection.

If, for example, this is the 10 A.M. medicine round, the nurse will examine the medicine-sheet of every patient who has a tick entered in one of the two 10 A.M. squares on the indicator strip. The necessary drugs can thus be quickly assembled on the trolley; and the nurse, together with the person who is to check the doses, can start the round. The first patient's sheet is on the top of the file; and the other sheets are in the order in which the ward round proceeds. As the trolley arrives at each bed, the patient's medicine-sheet must be consulted, irrespective of whether or not a tick is shown on the indicator strip. This eliminates the risk of error due to forgetting to mark the strip.

A further risk is that a prescription may not have been entered on the medicine sheet of the fold-flat file. In hospitals where treatment cards hang by the bedside nurses can check the entry on the medicine sheet against the prescription on the card during the medicine round; but, unfortunately, hospitals vary in their handling of treatment cards. If they hang at the bedside, it is found that there is a constant need to refer to them in the sister's office, and much time is spent in carrying them to and from the bedside. A satisfactory method is to use a light mobile file which is normally kept in the sister's office but which can travel round the ward with the ward rounds.

Injection rounds are carried out separately from the medicine rounds but they proceed in exactly the same way, observing the ticks in the shaded squares of the indicator strips when assembling the required injections and syringes. Should a patient be moved from one bed to another his medicine sheet is easily shifted in the fold-flat file.

This scheme was given a nine-month trial in a 35-bed medical ward and a 35-bed surgical ward; and it was found to be very satisfactory. It saves time at every stage of the medicine round, and it is much safer than the old system. It has now been introduced into all wards of this hospital, and has been running smoothly for some months.

In surgical wards the preoperative and postoperative drugs are regarded as part of the operation procedure and are not recorded in the file. Similarly, in the maternity unit the drugs administered during and immediately after labour are not recorded.

SURNAME SMITH — AGE 53 — WARD C — REG. NO. 143572

CHRISTIAN NAMES JOHN — CONSULTANT MR. JONES.

DRUG	DOSE	TIME (BD. TDS)	COMMENCED DATE	COMMENCED TIME	DISCONTINUED DATE	DISCONTINUED TIME	DOSE TIMES
INJ. PENICILLIN G	500,000 units	B.D.	3rd Oct	10 a.m.	7th Oct	6 p.m.	10 a.m. 6 p.m.
TAB. CODEIN. CO	1	TDS	4th Oct	10 a.m.	11th Oct	6 p.m.	10 a.m. 2 p.m. 6 p.m.

NAME	INJ. 10 A.M.	INJ. 12	INJ. 2 P.M.	INJ. 6 P.M.	INJ. 10 P.M.	INJ. 12 NOT.	INJ. 2 A.M.	INJ. 6 A.M.	NOTES
SMITH J	✓		✓	✓					

Fig. 3—The medicine sheet and indicator strip. The latter is replaced each time treatment is changed. The medicine sheet measures 8 × 5 7/8 in.

SCOPE FOR MODIFICATIONS

This scheme was designed solely to replace the medicine list; possible variations at once spring to mind.

1. Would it not be better for the doctor to write his prescription directly on to the patient's sheet in the file? The headings of the columns would have to be modified: a separate section would have to allow the sister to record the times, doses and other instructions to her nurses. It would be necessary to send the sheets from the file to the pharmacy for dispensing; and difficulties might arise from missing sheets during the medicine round. With this modification carbon copies would seem to be essential; and carbon copies increase the number of possible sources of error.

2. Could not a column be provided so that the prescribing doctor could countersign the sister's entry? This would mean that already overworked house-officers would have to sign each prescription twice; but this modification has undoubted merits.

3. Could not nurses sign for each dose of medicine administered? This was seriously considered and could work quite well in small wards. In large medical wards, however, the number of signatures collected would be enormous; and inevitably prescriptions would have to be transcribed again and again. This would reintroduce one of the risks we are trying to avoid.

4. Could the medicine file not be combined with the similar file kept for special nursing requirements—massage, feeding, and the like? The main objection to combining these two records is that the medicine file is in use for most of the day—during medicine rounds and injection rounds—and would not be readily available for other purposes.

I should like to thank Southmead General Hospital Group Management Committee for permission to publish this paper. I should also like to thank Mr. D. J. Britton for his assistance in devising the scheme and also the matron, sisters, and nurses for their cooperation in perfecting it. I much appreciated encouragement and constructive criticism from the medical staff.

Dialogues of Today

"GROW OLD ALONG WITH ME! THE BEST IS YET TO BE"

SOCRATES: I'm glad to see you about again, Nestor. Someone told me you had pneumonia.

NESTOR: So I had, Socrates; but Eryximachus here with his new magic pricked me into life again. Grateful though I am to him, however, I'm not sure that he has done me a service.

SOCRATES: Why not?

NESTOR: Pneumonia used to be called "the old man's friend", but it is no longer the obol paid to Charon for a quiet departure, and I suspect that Eryximachus has kept me alive only to develop in time some more unpleasant disorder for which he has no remedy. And I believe that if I had a stroke and got pneumonia again he would make sure I didn't die of it.

ERYXIMACHUS: Naturally, for it is a precept of Hippocrates, and a principle of true religion, that the doctor must always do all in his power to prolong life. If we had no such principle where should we draw the line? Are we to refuse to cure a young woman of appendicitis because she may die many years later from cancer?

NESTOR: I am not speaking of the young, Eryximachus, but of the old; and is it not true that you have in your hospitals more and more old patients who suffer from permanent and distressing disabilities because modern medical treatment has saved their lives in the past?

ENTHUSIASTICUS: Not only that, Nestor, but the consequences are quite paradoxical. For, these old people, who often need no more than simple nursing care, occupy beds in the most expensive hospitals for long periods, and thereby actually delay the admission of younger people, for whom much more could be done.

ERYXIMACHUS: It is true that we haven't as yet adequate provision for the growing number of disabled old people, but that is another problem. We cannot help it if advances in medicine occur faster in some spheres than others. What we need now is more knowledge about the causes and prevention of the diseases of old age, so that we may be able not only to prolong life but also to ensure that the life so prolonged is active and healthy.

SOCRATES: Do you think it likely, Eryximachus, that in time it will be possible to prevent strokes and to prevent or cure cancer?

ERYXIMACHUS: That is almost certain, Socrates, for the causes of strokes and cancer so far as we know are no different in kind from those of diseases which are already cured or prevented. All that we need is more knowledge of disordered physiology in order to prevent them too.

SOCRATES: And does that apply to many other diseases of old age?

ERYXIMACHUS: Certainly.

SOCRATES: And do human beings die of old age itself or only of the diseases which happen to occur in old age?

ERYXIMACHUS: As far as we know, only of diseases; for there is no recorded case of anyone, however old, dying without some disease to explain his death.

SOCRATES: So we may expect, may we not, that as medical science progresses human beings will live longer and longer? Is it possible that eventually some may live indefinitely?

ERYXIMACHUS: It is certainly theoretically possible.

SOCRATES: Now you must enlighten me, Eryximachus, on a question which puzzles me. You tell me it is a principle of religion that life should be prolonged whenever possible. It would follow, would it not, that it is a religious duty to do all that is possible to prolong life indefinitely?

ERYXIMACHUS: So it would seem.

SOCRATES: But does not religion also teach that this life is a preparation for another, and, as some hope, a better one?

ERYXIMACHUS: Yes indeed.

SOCRATES: Tell me then, which man can the more reasonably wish life to be prolonged indefinitely—the religious man, who looks forward to a better one, or the unreligious man who believes that this life is all?

ERYXIMACHUS: The unreligious man.

SOCRATES: But if it is a religious principle that the doctor must do all in his power to prolong life, is not the unreligious man in this matter imbued with a religious principle, and the religious man putting into practice the beliefs of the unreligious one?

ERYXIMACHUS: Apparently so.

SOCRATES: Tell me something more. If we prolong life and postpone death will there be more people in the world than there were before?

ERYXIMACHUS: Obviously, if people continue to be born.

SOCRATES: In that case the population of the world will go on steadily and ever more rapidly increasing. But if the old were to live on indefinitely, and the birth-rate were to be restricted accordingly, would not the world be populated by the same people growing older and older?

ERYXIMACHUS: That also must be true.

SOCRATES: Which course do you think the more consonant with true religion? Or can it be that when you cured Nestor's pneumonia you had not considered all the implications of the principle you were applying?

Medicine and the Law

Hospital's Claim against Insurance Company

G., who was injured while a passenger in a motorcar, was admitted to hospital and given treatment. The expenses incurred by the hospital for treatment were £12 12*s.* 6*d.* At the time of the accident the driver of the car was insured for all liability as required by section 36 (1) (*b*) of the Road Traffic Act, 1930, and also against liability to voluntary passengers in his car. The driver's insurance company made a payment to G. in respect of his injuries. At the time they made it they did not know that G. had been treated in hospital, but they did know of it before the hospital issued the writ in this action claiming that they were entitled to recover the expenses they had incurred in treating G.

The hospital based its claim on section 36 (2) of the Road Traffic Act, 1930 (as substituted by section 33 of the Road and Rail Traffic Act, 1933, and applied by schedule 10 of the National Health Service Act, 1946) which provides that "where any payment is made . . . by (*a*) an authorised insurer under or in consequence of a policy issued under . . . this Act; or . . . in respect of . . . bodily injury to any person arising out of the use of a motor vehicle on a road . . . and the person who has been so . . . injured has to the knowledge of the authorised insurer . . . received treatment at a hospital in respect of the injury so arising" there shall also be paid by the authorised insurer to the appropriate regional hospital board the expenses reasonably incurred by the hospital in affording such treatment limited to £50 for inpatients and £5 for outpatients.

Mr. Justice SALMON said that there was no reason why a policy which gave the cover required by the Act and complied with all the requirements of the Act should fail to qualify as a policy issued under the Act merely because it included cover beyond that made compulsory. Therefore the payment made to G. by the insurance company (who were admittedly authorised insurers) was a payment made in consequence of a policy issued under the Act.

Prima facie, G. was clearly "any person" within the meaning of section 36 (2). The insurance company had urged that "any person" meant any person of the class required to be covered by the Act but the words used in the section were as wide as they could be. The object of Parliament in passing the Road Traffic Acts was to protect not only third parties injured in motor accidents but also the hospitals who treated them for their injuries. There was no reason why the provisions of section 36 (2) should be confined to persons compulsorily insured and exclude voluntary passengers. The hospital treatment was no less valuable to the voluntary passengers than it was to any other third parties. Moreover the insurance companies obviously benefited; but for such treatment injuries would have graver consequences and damages payable by the insurers would be higher. He held that the words "any person" in section 36 (2) included voluntary passengers.

His Lordship said that those conclusions could not affect the result of the case having regard to the view he had formed on the final point argued, which concerned the provision in section 36 (2) that the person injured had "to the knowledge of the authorised insurer" received hospital treatment. The contention that that meant that the knowledge need only precede the issue of the writ did not carry conviction to his mind. It was easy to see why Parliament should have made that provision because many thousands of claims by third parties were settled each year by insurance companies, and they had to assess their possible total liability. It would be a hardship if, after paying out a sum to avoid litigation in ignorance of a person's having hospital treatment, the insurers should have to pay out a further sum in respect of such treatment. There seemed no reason for the legislature to insert a provision as to the knowledge of hospital treatment unless the knowledge was to precede the payment to third parties. Accordingly, since it was admitted that the defendants did not know of the hospital treatment until after they made their payment to G., they were under no statutory obligation to pay the expenses of that treatment to the hospital. There would be judgment for the insurance company.

Barnet Group Hospital Management Committee *v.* Eagle Star Insurance Co., Ltd.—*Queen's Bench Division* (Salmon, J.): July 30, 1959. Counsel and solicitors: J. R. Cumming-Bruce (Merton Jones, Lewsey, & Jefferies); Gerald Gardiner, Q.C., and Michael Lee (Simmons & Simmons).

E. M. WELLWOOD
Barrister-at-Law.

Public Health

PNEUMONIA AND ATMOSPHERIC SULPHATE DEPOSIT

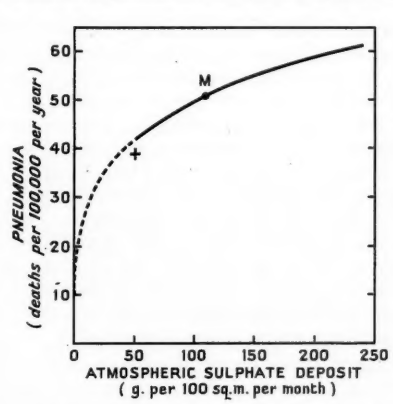
EVILLE GORHAM*
M.Sc., Ph.D.
LATELY ECOLOGIST, FRESHWATER BIOLOGICAL ASSOCIATION, AMBLESIDE, WESTMORLAND

THE fact that pneumonia mortality is higher in urban areas suggests that air pollution has some effect upon the incidence of this disease.

To test such a possibility, pneumonia mortality-rates were calculated for the whole populations of fifty-three county and Metropolitan boroughs in England, Scotland, and Wales, from the Registrar General's annual statistical reviews for the 5-year period 1950–54. These rates were then plotted against the pH of the precipitation, and the atmospheric deposit of tar, ash, other combustible material, and sulphate, using data for single stations and periods within these boroughs taken from the 27th report of the Department of Scientific and Industrial Research on the investigation of atmospheric pollution (1955).

From this preliminary study it was evident that the only one among these components of air pollution showing any obvious relation to pneumonia mortality was

* Present address: Department of Botany, University of Toronto, Canada.



The relation between pneumonia mortality and winter sulphate deposit in urban areas. M gives the logarithmic mean urban death-rate, and the dotted line extrapolates the curve to low levels of sulphate deposit. Both the average rural sulphate deposit and the rural death-rate from pneumonia are marked by the cross.

sulphate deposit, which presumably depends mainly upon the emission of sulphur dioxide from burning coal.

The correlation of pneumonia mortality with sulphate deposit was then calculated statistically, using the 5-year mortality-rates and the averages of all the sulphate figures given for each of the boroughs during the winter months September to March, when air pollution is usually much worse than in summer. A logarithmic transformation of both variables was made in order to provide more normal frequency distributions and, as far as could be seen, a more adequately linear regression.

The correlation coefficient (r) so calculated is $+0{\cdot}35$, a highly significant value ($P=0{\cdot}01$). The regression equation for the relation between pneumonia mortality (p, as deaths per 100,000 of population per year) and winter sulphate deposit (s, as g. per 100 sq. m. per month) is $p=16s^{0{\cdot}25}$.

This relation is shown graphically in the figure, which also shows the death-rate for rural areas in England and Wales over the same period.

It will be seen that the logarithmic mean urban death-rate of 51 per 100,000 persons per year is some 30% higher than the rural death-rate of 39. It must be borne in mind, however, that in Britain the rural population, too, is subjected to air pollution, with the average sulphate deposit in areas outside the main centres of population and industry being about 50g. per 100 sq. m. per month (Meetham 1950). (This is in fact a whole-year average, but according to table 3 of the 27th report of the Department of Scientific and Industrial Research the winter values are not much different from the summer ones where the deposit is low.) Meetham estimates also that the average life of a sulphur-dioxide molecule in the air is about 12 hours, by which time it may well have travelled far from its urban point of origin.

In view of the exposure of the rural population to considerable air pollution, it is of interest to extrapolate the curve backward to lower levels of sulphate deposit along the dotted line calculated from the equation given above. This extrapolation suggests (although the interpretation cannot be regarded as other than highly speculative) that reduction of sulphur pollution might appreciably reduce pneumonia mortality. This presupposes that the correlation is causal, which of course may not be so, although most investigators think that sulphur dioxide in high concentration has ill effects.

In connection with the association between certain diseases and air pollution, a previous investigation (Gorham 1958) showed a highly significant correlation between bronchitis mortality and the pH of precipitation in the same districts as those examined here. Pneumonia mortality, however, shows no apparent correlation with rain pH, nor, after partial correlation, did bronchitis mortality show a significant correlation with sulphate deposit. The reasons for this difference are obscure, but it seems possible that the ærosol droplets carrying the hydrogen ions are deposited in the bronchi, and do their damage there, while the sulphur, in the form of gaseous sulphur dioxide, penetrates farther and exerts its deleterious effect in the lungs themselves.

I am indebted to Mr. David Driver for much of the tabulation and computation.

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In England Now

A Running Commentary by Peripatetic Correspondents

EVERY year we spend our holidays in a remote corner of Dorset, where our host, Billie, has lived in Winspit Cottage for all his 73 years. Life there is epitomised by the privy; it is sturdily built, ivy-covered, and stands apart in the corner of the garden wall. There are no pipes or chains, but a seat with a bucket under. Here we used to relax, until on the third day of the holiday my wife entered in her bathing costume. She left the door open, the better to enjoy the sunshine and to allow egress of coprophilic flies. Not till she was seated did she notice an adder climbing the wall less than six inches from her left leg.

Description here lags sorefoot behind events. Qualifying for the Olympic hop, step, and jump, she cleared the threshold and four paving-stones in one leap. Choking with tachycardia she turned to verify her experience, thanked Æsculapius for her escape, and drew the fetters of her bathing costume upwards from her ankles. Walking now, she felt more composed; she was able to find Billie in his garden. He, with the countryman's certainty that nothing evil will be in a hurry to depart, sauntered to the privy and scotched the snake. "Thik bloody adder had enough poison in it to kill twenty dozen full-grown people."

Such exaggeration escaped our notice until we heard the story in the *Square and Compass* at opening time. Even so, the damage was done; viper-ileus was established in all members of the family and even the three-year-old can only with difficulty perform in the comfort of the nearest flush lavatory, owned by our friend, the surgeon. He intends to use my wife's discomfiture to illustrate his lecture next year on a hitherto unrecognised cause of changed bowel habit.

Billie is discomposed by the stir of events. "Never," he says, "has an adder been in thik lav in my lifetime. He must 'ave come over the hill and lost his way."

* * *

The fæcolith that was the size of an *American* golf-ball reminds me of the student who described a tumour as "the size of a *small* golf ball". The surgeon made full use of the opportunity to point out the foolishness of such a term, the importance of accuracy in clinical notes, and so on and so forth. The student, however, bided his time and at a later ward round described an excrescence, quite accurately, as "the size of a snipe's egg". In the words of Bernard Miles "That 'ad 'im".

* * *

Overheard in the waiting-room.—"Mummy has gone to hospital to choose a new baby. She will have to stay a few days because there are so many to choose from, and when she's chosen the sort she wants she will have to stay a bit longer to learn how to use it."

* * *

THE NEW JERUSALEM
or
FAREWELL TO THE BOARD OF CONTROL
(*A Fragment*)

Scene.—A nonmentalhospital (just like any other hospital, except, of course, for the location, architecture, layout, equipment and maintenance rate).

Time.—The Appointed Day.

Characters.—The nonmedicalsuperintendent in conference with the group secretary. They have just been liberated from the shackles of an outmoded legal and administrative system. They look worried.

Nonmedicalsuperintendent (to group secretary):

Bring me my robe of shining white!
Bring me my specs of roseate pink!
It *will* be "all right on the night"
(I'm sure it will . . . I hope . . . I *think*)
Still, if we do get in a jam,
We know that we can always ring
The—What? See section two? Oh, damn!
The Act's *dissolved* the wretched thing!

Letters to the Editor

A COLLEGE OF PATHOLOGISTS

SIR,—I am glad Peter Davey (Aug. 29, p. 231) is sensible of the aspirations and ambitions of the young pathologists in this country. They are already beginning to hear of the success of the Colleges of Pathologists in Australia and America, and they look forward to the day when there will be a similar college in this country. These colleges have already done much to raise the status of pathology in their countries: to encourage the proper training of young pathologists, to set qualifying examinations recognised by all their hospitals, to bring together the widely separated branches of pathology, and to give an esprit-de-corps which would be very helpful over here.

I am tired of hearing how we should join with the Royal College of Physicians of London. Why London? Surely Edinburgh would be more suitable. After all Scotland is the cradle of pathology in this country, and Edinburgh has always been helpful to the young pathologist in search of a qualification. And why Physicians, pray? Most of our work is done for surgeons and gynæcologists. Surgeons have always been kind and generous to their colleagues, and the careful examination of surgical material in this century has given us a clearer and more accurate picture of disease than we have ever had before.

Surely the only way of solving our present dilemma—of the older pathologists preferring the College of Physicians, and many of the young pathologists being increasingly attracted to the College of Surgeons—is to found our own college, where all pathologists can find a true home. The cry of the young pathologist today is, "How long, O Lord, how long?"

Westminster School of Medicine,
Research Laboratories,
London, S.W.1. JOHN S. CORNES.

PENICILLIN IN LEPTOSPIROSIS

SIR,—In the past few months two letters in your columns have suggested that penicillin is beneficial in the treatment of leptospirosis in Malaya.[1 2] This is in spite of exactly the opposite conclusion reached from a controlled clinical trial in the same country by Dr. Fairburn and myself.[3]

The opinions expressed by Lieut.-Colonel Mackay-Dick and Captain Robinson are based largely on information contained in their article of 1957.[4] This offers, in my opinion, no reliable evidence as to whether penicillin was useful or not.

In assessing the benefit of any form of treatment of leptospirosis there are three useful guides: (1) duration of fever; (2) duration of symptoms; and (3) incidence of the jaundice and oliguria (or anuria).

Mackay-Dick and Robinson[4] found that the duration of fever was reduced from an average of about thirty-four hours to about eighteen hours. The controls, however, were patients treated by Colonel Mackay-Dick's predecessors in Malaya at a different period and with a probably different distribution of serological types. In a disease of such variability control and treatment must coincide, and one must know more exactly the criteria for selection of controls, their numbers, and the results of statistical analysis. In the absence of this information the significance of a mean reduction of sixteen hours in the duration of fever cannot be assessed.

The effect that penicillin may have had on the duration of symptoms is even more difficult to judge. No figures for the total duration of symptoms are included as in the other two trials performed under similar conditions in Malaya.[3 5] Only by day-to-day recording of symptoms, on *standard* charts by the same observers, can their duration be assessed with any confidence. To make comparison valid this has to be done in the same way for controls and treated patients.

Finally in the series of Mackay-Dick and Robinson the incidence of jaundice was 21% and of oliguria 6%. The corresponding figures for the *controls* (31 cases) in Fairburn and Semple's series were 7% for jaundice and 7% for oliguria.

The dose of penicillin given in the first five days by Mackay-Dick and Robinson was 13·2 million units as opposed to 12·0 million by Fairburn and Semple. Treatment was continued for seven days in the former trial and for a mean of six days in the latter. Hence a criticism of insufficient penicillin is unjustified.

Major Cook[2] says that the regime described by Mackay-Dick and Robinson has become the standard in military hospitals in Malaya. If this is correct it means that the evidence from a "personal experience" trial has been preferred to the evidence from a controlled trial. It is really rather sad that this should happen in a country which probably leads the world in the planning and evaluation of therapeutic trials. Members of the profession must now be well aware that such trials have exploded many "therapeutic myths".

Both animal experiments and study of the disease in man provide ample reason for questioning the efficacy of penicillin against leptospirosis.[3]

Briefly, animal experiments showed that penicillin, to be effective, must be given early—probably within twenty-four hours after inoculation. If these findings are applicable to man, treatment would have to anticipate the dissemination and multiplication of leptospiræ in the tissues, which normally takes place during the incubation period of four to twelve days. In practice treatment is seldom started before the fourth day of the disease and often later. Broom[6] reviewing the results of penicillin therapy in 206 patients in this country found no significant difference in mortality compared with 259 patients not given penicillin. Hall et al.[7] reported on 79 cases from an epidemic in Puerto Rico and found no significant effect of penicillin on fever, jaundice, renal involvement, or leptospiræmia.

However, whatever view is held on this matter, the fact remains that a properly controlled trial has been done.[3] The only way in which this can be refuted is to show some fundamental defect in the trial, or to produce contrary evidence from another equally or better controlled series.

Department of Medicine,
St. Thomas's Hospital
Medical School,
London, S.E.1. S. J. G. SEMPLE.

SCRAPIE AND KURU

SIR,—While attempts to draw too close an analogy between diseases of man and lower animals are attended by numerous pitfalls, many valuable clues contributing to the understanding of the fundamental nature of a disease can be gained from a broad comparative viewpoint.

With this in mind, I should like to present a few brief comments on the similarity of two progressive degenerative disorders of the central nervous system—namely, scrapie[8] affecting sheep, and kuru[9] affecting the Fore natives in the Eastern Highlands of New Guinea. I do not suggest that these diseases are identical or even

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2. Cook, A. T. *ibid.* 1959, ii, 81.
3. Fairburn, A. C., Semple, S. J. G. *ibid.* 1956, i, 13.
4. Mackay-Dick, J., Robinson, J. F. *J. R. Army med. Cps*, 1957, **103**, 186.
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counterparts, but in my opinion their overall resemblance is too impressive to be ignored. (The contention that scrapie is a myopathy [10] has not been corroborated by the observations of others [11 12] or by my studies.)

When viewed collectively, the general epizootiological, ætiological, clinical, and pathological features of scrapie closely parallel those that characterise kuru, as recently described by American [9] and Australian [13–15] investigators. Thus, each disease is endemic in certain confined populations, whether this be flock or tribe, in which the usual incidence is low—about 1–2%. Sheep, or persons, may become clinically affected months after they have been moved from flocks, or communities, where the respective disease is endemic. Moreover, scrapie may appear in a previously non-affected flock following introduction of a ram or ewe from a flock in which the disease is known to exist. Likewise, kuru may be introduced through marriage to populations previously free of the disease. Yet, despite these well-established observations, the exact mechanism underlying the "spread" of scrapie or kuru is obscure; certainly evidence that contagion is responsible is either equivocal or non-existent.

The cause of each disease is obscure. No microbiological agent has been isolated, nor is there convincing evidence that either scrapie or kuru is an infectious disease in the generally recognised sense. Nutritional and toxic factors have not been incriminated as having ætiological significance in either disorder. However, a genetic predisposition is strongly suggested by the accumulated epidemiological and epizootiological data.

The natural history and general clinical aspects of the two diseases are strikingly similar. Onset of each disorder is insidious, and occurs in the absence of signs of antecedent illness. The course is afebrile, and almost invariably is relentlessly progressive. Both diseases usually end fatally within three to six months after onset; only rarely have remissions and recoveries been observed. Detailed consideration of individual clinical signs and physical findings seems less important in illustrating the broad similarity, for these features are largely reflections of variations in the characteristic distribution of the lesions and in the functional development and integration of the nervous systems of the two species. Nevertheless, such signs as ataxia, which becomes progressively more severe, tremors, and changes in behaviour are features of both diseases. In neither case have laboratory studies revealed regular or significant abnormalities in the blood or cerebrospinal fluid.

Lastly, the neuropathological changes, though essentially non-specific, are remarkably similar in the two diseases. Widespread neuronal degeneration, largely characterised by shrinkage and hyperchromia of the cell body and by various degrees of vacuolation of the cytoplasm, is typical of both disorders. Astrocytic gliosis, often of pronounced intensity, is another common feature, as is minimal degeneration of myelin in some instances. Inflammatory changes of the extent and severity usually associated with an active encephalitic process are not observed. Large single or multilocular "soap-bubble" vacuoles in the cytoplasm of nerve-cells have long been regarded as a characteristic finding in scrapie; this extremely unusual change, apparently seldom seen in human neuropathological material, also occurs in kuru,[15] and first aroused my curiosity about the possible similarity of the two diseases.

This brief comparison of scrapie and kuru is presented not merely to enumerate interesting similarities, but, more significantly, to indicate an intriguing implication when the analogy is viewed against the background of data on experimental investigations of scrapie. Despite the lack of indications suggesting that scrapie is an infectious disease, the disorder can be induced experimentally in the sheep [8 16] and in the closely related goat [17] (but not in other species so far tested) inoculated intracerebrally or subcutaneously with suspensions of brain tissue, as well as certain other tissues, from scrapie-affected sheep. Strangely, clinical disease never appears in inoculated animals in less than three and a half months and may not become evident in some animals until thirty months after inoculation. The nature of the pathogenetic factor in the inoculum and the fundamental biochemical alteration that gives rise to the disorder in the inoculated animal remain to be elucidated. Nevertheless, such experimental induction of a progressive degenerative disorder of the central nervous system and its successful "transmission" in series would seem to provide a valuable clue to the eventual understanding of the broadly similar and equally perplexing human neurologic disorder represented by kuru. Thus, it might be profitable, in view of veterinary experience with scrapie, to examine the possibility of the experimental induction of kuru in a laboratory primate, for one might surmise that the pathogenetic mechanisms involved in scrapie—however unusual they may be—are unlikely to be unique in the province of animal pathology.

Agricultural Research Council
Field Station,
Compton, near Newbury, Berks. W. J. HADLOW.

10. Bosanquet, F. D., Daniel, P. M., Parry, H. B. *Lancet*, 1956, ii, 737; leading article, *ibid.* p. 767.
11. Palmer, A. C. *Vet. Rec.* 1957, **69**, 1318.
12. Hulland, T. J. *J. comp. Path.* 1958, **68**, 264.
13. Bennett, J. H., Rhodes, F. R., Robson, H. N. *Aust. Ann. Med.* 1958, **7**, 269.
14. Simpson, D. A., Lander, H., Robson, H. N. *ibid*, 1959, **8**, 8.
15. Fowler, M., Robertson, E. G. *ibid.* p. 16.
16. Gordon, W. S. *Vet. Rec.* 1957, **69**, 1324.
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POTASSIUM-SECRETING TUMOURS OF THE LARGE INTESTINE

SIR,—In their article of April 11 Mr. Roy and Mr. Ellis cited their experience with potassium-secreting tumours of the large intestine. We would question the term "potassium-secreting tumour" used by them and earlier by Cooling and Marrack,[1] since their data and those of other investigators provide little evidence that excessive amounts of potassium are lost as a result of the secretion of this ion by the tumour per se rather than as a result of diarrhœa. To justify such a term, it would be important to demonstrate that the tumour itself is secreting sufficient potassium to cause the deficiency.

In the cases reported by Roy and Ellis, and those referred to in other articles, all the individuals studied had severe diarrhœa. With the exception of the original report by Starr et al.,[2] all the cases had a potassium concentration per litre of rectal fluid essentially equal to that seen in patients with diarrhœa from other causes. Diarrhœa fluid in patients without this tumour often contains from 10 to 50 mEq. of potassium per litre. Patients with diarrhœa due to salmonella infections, typhoid fever, ulcerative colitis, and partial obstruction of the rectosigmoid colon (diverticulitis, adenocarcinoma, or irradiation cicatrisation) also have potassium losses in the fæces of this magnitude. Roy and Ellis reported that the mucus from the villous tumour contained only 1·8 mEq. of potassium per litre while the rectal fluid had 17·6 mEq. per litre. The latter value is well within the range for diarrhœa fluid. Starr noted that the mucus secreted by the tumour contained 80 mEq. per litre. Whether or not the mucus was contaminated with blood-cells or colonic debris was not discussed, but such factors must be considered in trying to explain the high value.

Since all the reported cases had villous tumours and diarrhœa, it seems obvious that by partial obstruction or irritation the tumour caused the diarrhœa. This uncompensated loss of water and electrolyte, whether caused by cholera, diverticulitis, or villous polyp, could be expected to produce dehydration and disordered serum-electrolyte values.

There is no more justification for concluding that these tumours secrete excessive amounts of potassium than there is for contending that ulcers which obstruct the pylorus secrete chloride. To prove that the potassium loss was directly due to the tumour, rather than to diarrhœa, it would be necessary to show that such a patient continued to lose large amounts of

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2. Starr, A., Mueller, S., McKittrick, J. R. *Arch. Surg., Chicago*, 1956, **73**, 995.

fluid and potassium per rectum when a colostomy proximal to the tumour diverted the fæcal stream. Although this has not been done, Starr et al. did report that their patient showed much improvement after they performed a temporary proximal diverting colostomy. They said that the fluid and electrolyte derangement was easily managed in spite of the fact that the mucus-secreting tumour was still present.

In most of the patients reported, considerable dehydration and often prerenal azotæmia has been evident. In some hyponatræmia has been quite striking, and hypokalæmia absent. Instead of using the term " potassium-secreting tumours ", which obscures the basic problem, it seems preferable to employ the terminology of previous authors; villous adenoma of the colon associated with severe hypopotassæmia,[2] or villous papilloma of the rectum with severe fluid and electrolyte depletion.[3]

Department of Surgery,
Western Reserve University,
Cleveland, Ohio.

WILLIAM E. ABBOTT
STANLEY LEVEY
JOHN BRADSHAW.

INHIBITION OF GLYCOGENOLYSIS WITH TOLBUTAMIDE IN LIVER SLICES

SIR,—Investigations to explain the mode of action of oral antidiabetic compounds are far from complete. Although these substances lower the blood-sugar level only in the presence of insulin, several facts seem to indicate that they exert their effect—at least partly—through the inhibition of glycogenolysis in the liver.

Several authors have approached the problem by studying their effect in separate phases of the enzymatic function of liver cells. In-vitro and in-vivo experiments, however, produced divergent data.[4–7]

We wanted to determine whether postmortem glycogenolysis could be influenced by oral antidiabetics. The glycogen content of the liver is known to decrease rapidly after death, so we decided to see whether tolbutamide would delay this. The method of our previous experiments [8] was used and the glycogen content of tolbutamide-treated rats' liver slices was compared with that of controls. Male albino rats, weighing 120–150 g., which had been starved for 24 hours were used. Two rats were given 25 mg. of tolbutamide through a gastric tube, and two were given physiological saline solution in each experiment. 4 hours later the animals were decapitated and six liver slices were taken from each. Two slices from the tolbutamide-treated rats and two slices from the control rats were put in the hot alkali solution immediately, two pairs of liver slices 10 minutes later and the rest in the 15th minute. Glycogen was determined by the method of Good et al.[9] As these experiments were comparative studies only, the excised liver slices were kept at room temperature, until the beginning of glycogen determinations.

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6. Ashmore, J., Cahill, G. F., Hastings, A. B. *ibid.* 1955, **6**, 744.
7. Vaughan, M. *Diabetes, N.Y.* 1957, **6**, 16.
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HEPATIC CONTENT OF GLYCOGEN (AS G. GLUCOSE PER 100 G. LIVER) IN CONTROL AND TOLBUTAMIDE-TREATED RATS

—	Glycogen content					
	Control rats			Tolbutamide-treated rats		
	At death	10 min. after death	15 min. after death	At death	10 min. after death	15 min. after death
Number of observations ..	21	21	17	22	22	18
Mean	1·2	0·8	0·7	1·3	1·2	1·2
Standard deviation	±0·5	±0·36		±0·74	±0·74	
Mean of the differences ..	−0·6			−0·07		
Standard error of the mean of differences	±0·07			±0·04		
t	8·57			1·75		
P	⩽0·01			<0·10		

Data (see table) were analysed as a series of differences (10-min. values minus initial values). The ' t ' value was determined by dividing the mean of the difference by the standard error. The difference between initial values was computed also by taking the means of the initial values of the treated and the control groups. The difference of the means was divided by the standard error, calculated from the standard deviation of the two initial series. The difference did not prove significant. ($t = 0{\cdot}5$; $P < 0{\cdot}50$.)

Our results indicate that in rats treated with tolbutamide the disappearance of glycogen from liver slices is delayed. In normal animals, on the other hand, the values diminish significantly both in the 10 and 15 min. periods. These observations seem to support the theory that oral antidiabetics inhibit hepatic glycogenolysis; nevertheless the autocatalytic decrease of liver glycogen is obviously not the same process as that which occurs in the living cell. We hope that further experiments will explain which enzymatic processes are involved here, and the nature of their connection with insulin.

Third Department of Medicine,
University of Budapest, Hungary.

ANTAL KÁLDOR
GÁBOR POGÁTSA.

IDENTICAL TWINS: AN ECONOMY IN CLINICAL RESEARCH

SIR,—Drug trials in psychiatry require strict techniques of control extended over long periods of time. This makes them difficult to devise and expensive to conduct. To obtain valid results large numbers of experimental subjects are usually required, many ratings have to be done which use up the researchers' time, large quantities of drugs may be needed, and what is most expensive of all and easily forgotten is the time of nurses who must administer the drugs and also observe the patients. There are many sources of error. The longer the duration of the trial, the greater these errors are likely to become. Changes in ward environment which are difficult for the unsophisticated observer to recognise are a frequent cause of confusion. These may range from changes in the relationship of staff working on the ward to those seasonal variations in climate which can be found very dramatically in Western Canada. All may greatly effect the lives of patients and their responses to treatment.

These sources of error can be minimised by conducting the trial so that both experimental and control groups of patients are on the same ward, are given their medication (drug or placebo) over the same period of time and are cared for by specially selected staff. The equivocal and often conflicting results in the literature show that psychopharmacological experiments of this sort which continue over weeks or months are far less easy to conduct than those " acute " experiments for which these techniques were originally devised. One wonders whether other techniques could not be devised which would allow us to find out more with greater sureness and at less expense.

Beveridge [10] suggested that in biological research an economy of numbers might be achieved by using identical twins, one member of the twin pair acting as control for the other. To support this suggestion he quotes livestock experiments undertaken in New Zealand.[11] For instance, in an experiment involv-

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11. Annual report, New Zealand Department of Agriculture, 1947-48.

ing butterfat yields, the results from one pair of identical twin cows were as valuable as those obtained from two groups of 109 cows each. For growth during the first year of life one pair of identical twin calves gave results whose significance was equivalent to at least 25 pairs of ordinary calves. The usefulness of identical twins has also been shown in other areas such as fertility investigations in bulls.

The classic work of Kallmann [12] and Eliot Slater [13] on the relation of heredity to mental disorder is well known. One feels that implicit in the work of these highly sophisticated writers is the idea that identical twins might prove admirable subjects for a variety of therapeutic trials—but this is never stated explicitly. The psychological literature describes many experiments designed to explore the relationship of nature and nurture in humans by means of twin studies. We have, however, been unable to find any report in the psychiatric literature on the use of twins in therapeutic trials using drugs or other procedures. Those who work with psychotomimetic agents seem to have neglected this approach also.

This is a strange oversight, because it seems that twin pairs used in this way might be of even more relative value than in those animal experiments to which we have already referred. In pure breeds of livestock one would expect that there would be a greater degree of genetic homogeneity than among humans and so relatively less benefit would be gained by the experimenters. Not only are humans inherently more variable but the type of inbreeding which is possible among cattle is socially prohibited, and so more control would be gained by twin studies involving humans. Naturally this would have to be confirmed experimentally.

It would be unreasonable to suggest using identical twins in clinical research without discussing their frequency in the population at large and also in mental hospitals.

Slater found that the incidence of twinning in mental-hospital populations, estimated at 2·2%, corresponds closely with that of the general population. He also found that the proportion of uniovular or identical twins accords with expectation—i.e., 24% of the twin population. Thus one might expect to find 5 patients who are members of identical twin pairs in a hospital population of 1000. If all 1000 patients were schizophrenic one would still expect to find 5 identical twins although there would not necessarily be a twin pair among these 5. If we take the concordance-rate for schizophrenia in identical twins as 80% (this being a rough mean of Kallmann's 86% and Slater's 76%) we might expect 4 of these 5 to be one of a pair concordant for this disease. Furthermore, Slater has shown that among uniovular twins who were concordant for schizophrenia, 32% develop the disease within one year of each other and 50% develop it within two years.

There are, of course, many factors which reduce the chances of both members of a twin pair being in the same hospital at the same time. The mobility of modern man is not the least of these; yet in spite of this it seems likely that there are many more twin pairs readily available for experimental and therapeutic trials than we have hitherto supposed. However, they are still not as common as researchers might hope, so that when they are found we suggest that they should be treated as " pure gold ".

Apart from fairly straightforward tasks such as comparing the effects of new phenothiazones with those of their parent drug, in large centres like New York and London where there may be 20 or 30 schizophrenic twin pairs under treatment at the same time, it should be possible to develop more refined and reliable assessments of the many new substances supposed to help psychiatric illnesses. If, in such regions, using a " twin index " similar to that which Kallmann has developed in New York, all affected twin pairs could be gathered together in the same research unit, we believe that much could be learned in a short time and at low cost. The twins themselves would benefit from the special care and attention which they would thereby receive.

12. Kallmann, F. J. Heredity in Health and Mental Disorder. New York, 1953.
13. Slater, E. *Spec. Rep. Ser. med. Res. Coun. Lond.*, 1953, no. 278.

We therefore suggest that Beveridge's hint can be used to reduce greatly the cost, in money, time, and labour, of drug trials in psychiatry by using matched pairs of identical twins who are concordant for the disease being investigated. A modification of this same technique has exciting possibilities in working with psychotomimetic substances. Identical twins are not uncommon in both general and psychiatric populations. While we are here concerned with clinical research in psychiatry, it is likely that the principles we have discussed could be fruitfully applied in other fields of medical research where drug trials are undertaken.

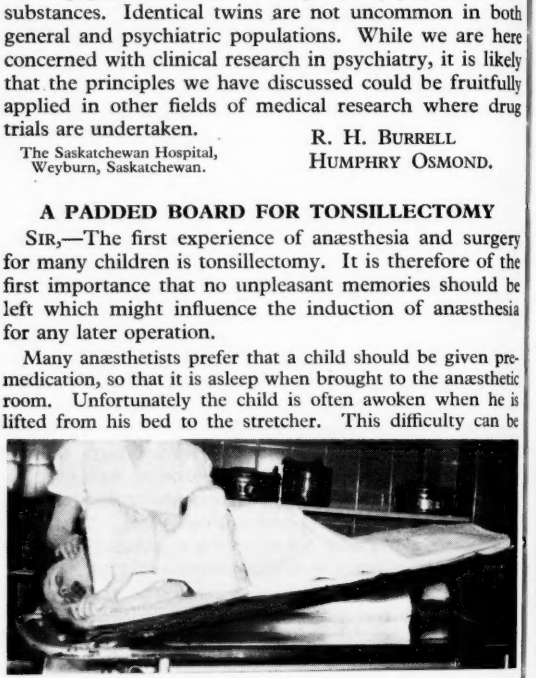
The Saskatchewan Hospital, Weyburn, Saskatchewan.

R. H. BURRELL
HUMPHRY OSMOND.

A PADDED BOARD FOR TONSILLECTOMY

SIR,—The first experience of anæsthesia and surgery for many children is tonsillectomy. It is therefore of the first importance that no unpleasant memories should be left which might influence the induction of anæsthesia for any later operation.

Many anæsthetists prefer that a child should be given premedication, so that it is asleep when brought to the anæsthetic room. Unfortunately the child is often awoken when he is lifted from his bed to the stretcher. This difficulty can be



overcome by inserting a padded board under the child in bed before premedication starts. The board is the same size as the top of the operating table and is provided with lifting handles; the child remains on it throughout the operation, during the journey back to bed, and until recovery of consciousness. A further advantage of the board is that it prevents sagging of the child's head when he is lifted on and off the operating-table. The board is provided with a hinged flap which can give a head-down tilt if necessary, so that any blood drains out of the mouth.

The illustration also shows an H-shaped padded piece of wood, designed to replace the inefficient pillow commonly used. This piece of wood is heavy, and when placed in position is not easily dislodged. It keeps the arms in the proper position, and can also be used to give support to the jaw.

I am indebted to Mr. D. Burningham for making the equipment, and to Mr. D. Ellis for the photograph.

London, N.W.3. MASSEY DAWKINS.

EFFECTS OF IRRADIATION ON SPECIFIC RENAL FUNCTIONS

SIR,—The preliminary communication of Dr. Klapproth and others (Aug. 22) will be valued particularly by those interested in the problem of preparing a patient to receive a functioning organ homograft such as the kidney.

When considering their results, however, it must be remembered that a kidney cannot be regarded as normal in the weeks following opposite nephrectomy. It must be expected to show the microscopic and functional changes of adaptive response to its increased excretory load. I believe these changes to be the same however they are effected.

Dr. A. A. G. Lewis and I have studied those resulting

from reabsorption from long ileal segments in the dog.[1] There appears to be a progressive increase in plasma clearance up to about the eighth or tenth week after the kidney is exposed to increased load. The reduced clearances observed by Dr. Klapproth after irradiation, therefore, gain significance when they are compared, not with normal figures, but with the higher clearances expected from a kidney undergoing hypertrophy following opposite nephrectomy.

Royal Free Hospital, London, W.C.1. JOHN HOPEWELL.

NON-CLINICAL TEACHING POSTS IN THE COMMONWEALTH

SIR,—The Commonwealth Relations Office not infrequently receives requests from countries in S.E. Asia for the loan of professors of non-clinical subjects for their universities and medical colleges under the Technical Cooperation Scheme of the Colombo Plan.

Delays frequently result while universities and other interested bodies are circularised.

Readers or senior lecturers on temporary secondment are preferred, but recently retired professors or lecturers in anatomy, physiology, pharmacology, pathology, bacteriology, and biochemistry are also acceptable in most cases.

For the sake of ready reference the C.R.O. is making a list of suitably qualified persons who would consider offers of such work on favourable terms. I should be glad if anyone interested in spending up to two years abroad in strengthening the bonds of the Commonwealth and in teaching their own subject would communicate with me at the Commonwealth Relations Office, Matthew Parker Street, London, S.W.1.

GEORGE MCROBERT.

DIMINISHED RESPONSIBILITY

SIR,—The idea behind the doctrine of diminished responsibility is that different degrees of culpability may attach to the same crime, according to the psychological reasons for its perpetration. This has been accompanied by a popular feeling that an explicable crime is less culpable than an inexplicable one. As Dr. Maddison (Aug. 15) has pointed out, however, psychological explanation cannot furnish us with much useful information about culpability, which is an ascientific, moral concept.

Dr. Maddison goes on to state his disbelief in "free-will", and summarily dismisses resistible impulses by reference to psychoanalytic doctrine—as though this was a fountainhead of scientific truth—by telling us that all impulses translated into action are by definition irresistible. This definition fails to account for the fact that we may give way to an impulse on one occasion and yet resist it on another. Yet this distinction is an important one, as I believe that the popular notion of culpability rests upon it.

Rape, assault, and poisoning the lodger may be taken as examples of culpable crimes. They are caused by low-level impulses such as greed and generalised lust, and they are thought of as culpable because the average man recognises these impulses in himself and resists them.

Less culpable crimes fall into two groups. To judge from reduced sentences that have recently been given, it would appear that killing one's girl friend when tragically in love with her, one's child when incurably ill and in pain, or one's wife when nagged to distraction are examples of crimes that are less culpable than the former group. This type of crime is motivated either by higher-level impulses, such as pity or love, or by prolonged and unusual stress. The average citizen has not experienced the extremes of these emotions, and feels uncertain whether he could resist them if he were to be subjected to them.

The other less culpable group covers those crimes that occur in psychotics, defectives, or those with brain diseases: psychiatric opinion is relevant and necessary in order to distinguish these cases. The idea of culpability can have little interest for the psychiatrist, whose attention would be more usefully employed in deciding what kind of treatment is likely to benefit the prisoner.

St. Thomas's House, London, S.E.1. D. P. GOLDBERG.

SIR,—In the hot and heady air of an August afternoon how welcome is the assurance of Dr. Maddison telling us that "Determinism must be accepted as the only valid scientific explanation of human conduct in all its complex facets". It is a gladsome thought that what we meant to do, but have not done, we could not have done.

A pity it is to leave the old-world calm of thirty years ago by reading modern scientific journals. We must forget Professor Brillouin writing:

"In many cases, strict causality must be replaced by statistical probabilities; a scientist may or may not believe in determinism. It is a matter of creed, and belongs to metaphysics; physical experiments are unable to prove or to disprove it."[1]

Perhaps psychiatrists take metaphysics in their stride in a way that physicists do not.

Norwich. T. D. F. MONEY.

JUNIOR HOSPITAL POSTS

SIR,—The medical staff committee of this hospital recently approached the medical schools in this country in an attempt to find out how many medical students would be expected to qualify this year, and how many posts would be available within the teaching hospitals for those who passed the necessary examinations.

Ten teaching hospitals were kind enough to reply; and on analysing their answers we learn that 705 medical students were expected to qualify, and for these successful candidates 658 posts were available in their respective teaching hospitals.

Information also has been obtained from the General Medical Council about the number of overseas doctors temporarily registered each year in this country, and it would seem that approximately 500 doctors are thus registered.

It is obvious from these figures that the junior hospital posts in provincial hospitals—were it not for the 500 overseas doctors—cannot be filled.

NORMAN KIMBELL
Chairman
H. J. RICHARDSON
Hon. secretary,
Medical Staff Committee.
Stamford and Rutland Hospital, Stamford, Lincs.

BOXING

SIR,—Referring to your excellent leader of June 6 on the dangers of boxing, it may be worth mentioning that boxing has been forbidden by law in Iceland since 1957. According to this law it is forbidden: (1) to hold public boxing-matches, (2) to teach boxing, (3) to import boxing-gloves and equipment for the teaching of boxing.

This law was proposed by two physicians who were then members of Parliament and who had made themselves acquainted with the literature on the dangers of boxing, especially the paper of Martland[2] in 1928 and

1. Hopewell, J. *Ann. R. Coll. Surg. Engl.* 1959, **24**, 159.

1. Brillouin, L. *Nature, Lond.* 1959, **183**, 501.
2. Martland, H. S. *J. Amer. med. Ass.* 1928, **91**, 1103.

the excellent exposition by Edith Summerskill in *The Ignoble Art* (London, 1956).

Besides the motives so rightly stressed in your editorial, with all of which I agree completely, we have observed an additional one, which should not be overlooked. It is not uncommon that young men, who have taken lessons in boxing, want to practise what they have learned. When we have learned something we all want to show our efficiency, and the boxer is no exception to this rule. This display of skill is especially to be expected when such a young man gets drunk. He may then attack an innocent person in the street, just to show how superior he is to other people in using his fists. And in general such people are more willing than others to start a fight, and for them a human head is first and foremost a target for blows.

It may of course be argued that the brains of boxers are not among the most valuable of the human race, and that one subarachnoid hæmorrhage more or less does not matter much. But, as you justly emphasise, the aim of the sport—to cause concussion, contusions, and hæmorrhages in the brains of other people—should be beyond the limits of sport. They are much too serious lesions for that. And even a boxer needs his brain and cannot afford to have any considerable number of his brain cells damaged.

Whatever value boxing may have in toughening and fortifying the muscles of a man is counteracted by its damage to the brain. Let us try to conserve the brains, which in a civilised community should deserve to be protected against the fists.

Department of Pathology,
University of Iceland,
Reykjavik.

NIELS DUNGAL.

ROLE OF THE PÆDIATRICIAN IN MENTAL ILLNESS

SIR,—Dr. Tizard and his colleagues (Aug. 29) have an excellent case, but they ruin it by overstatement. More and more doctors are now becoming aware that emotional disorders constitute an important if not major part of human illnesses, and are perhaps basic to all illness. And, as the pattern of emotional reactions is laid down in early childhood, pædiatricians certainly play an important part in prevention and treatment. They ought to know about, understand, and be skilled in dealing with emotional disturbances. But to claim that pædiatricians and family doctors should needs have a personal analysis as part of their medical training is certainly overdoing it. A personal analysis is a form of medical treatment that may be very good for an emotionally disturbed doctor, but in itself it will not help him in his work any more than any other form of therapy. Let us also not forget that a personal analysis may take from two to four years of daily analytic work, and that it may end up in failure. Psychoanalysis has its therapeutic failures, too.

The great danger of Dr. Tizard's proposition is that it may frighten doctors into thinking that only "experts" should deal with emotional disorders. It underlines an undesirable dichotomy of doctors into "haves" and "have-nots", which comes out clearly in Dr. Tizard's paper where he and his collaborators issue their stern warning to "psychologically untrained pædiatricians" who well may understand a child's emotional processes but who "will not know how to handle the situation; and this may lead to a painful and even damaging experience for the child". Do pædiatricians or family doctors who have not been analysed or have no formal psychiatric training really damage their patients, children or adults, by their handling of the emotional situation? I doubt it, because doctors have done it for centuries and do it all day long. We could all do better if we knew more about emotional processes, but that probably goes for Dr. Tizard and his colleagues, too. The primary and really important step is to realise that emotional processes exist and are vital in illness and in the doctor-patient relationship.

Dr. Tizard and his colleagues give a whole sackful of advice in their paper, culminating in the acme of advice that pædiatricians should not give advice to parents about the management of their children. Who really knows whether this is right? Let us discuss these questions and argue them out, but let us be aware that with our present very limited knowledge of emotional processes no authority, no psychological school, no possessor of diploma or degree can rightly make ex-cathedra pronouncements about our most fundamental professional activity—the handling of emotional situations within our patients and within the doctor-patient relationship.

What we need most at present is widespread interest by doctors in these situations, a willingness to recognise and understand them, and a willingness free from undue anxiety to handle them, to experiment and to research, untrammelled by obiter dicta.

Southall, Middlesex. MAX B. CLYNE.

SELECTION AT CELLULAR LEVEL AND THE ECOLOGY OF TUMOURS

SIR,—Surely most of what Mr. Michael Frost says in his letter last week is self-evident and has already been said.

He rightly remarks: "The question arises as to how the cell achieves adaptive variation," and then gives no kind of answer to the question. The answer is We don't know. Does Mr. Frost think it is Lamarckian—i.e., the environment alters the genic material of the cell so that an acquired characteristic is inherited? If so how does he explain the long latent period of carcinogenesis? Or does he think the genic change is a somatic mutation as it has been fashionable to think since Boveri put forward the notion in 1902? Or does he think that a virus in the cell multiplies at cell division and so gives the appearance of altering the cell's genic make-up?

I have pointed out the objections to all three of these explanations of cell variation [1] and submitted another view which seems to describe the facts.

Mr. Frost's last paragraph seems to contradict itself. If tumours arise at an age when they are likely to be "outselected", surely this would be the age when they are just the most likely not to arise.

London, S.E.3. G. E. LOXTON.

AN EXAMINATION PAPER FOR . . . ?

SIR,—Dr. Grant (Aug. 29) is not correct in saying that there are two mutually exclusive streams of nurse-training; a number of hospitals have dual training schools where the trainees are readily interchangeable. Neither does the State-enrolled assistant nurse have to start all over again if she wishes to become State-registered; she is given a concession period by the General Nursing Council.

London, W.C.2. P. D. NUTTALL.

1. Loxton, G. E. *Med. Pr.* Aug. 12, 1959; *ibid.* Aug. 26, 1959; *ibid.* (in the press).

TOXOPLASMA IN SHEEP

SIR,—I was very interested in your editorial and in the paper by Rawal (April 25), reporting a high incidence of toxoplasma parasites in brains of sheep. I should like to point out, however, that in spite of the superiority of the animal-inoculation technique for the demonstraton of toxoplasma, it is possible to find pseudocyts—some of which resemble toxoplasma—on histological examination of brains from apparently healthy sheep. Furthermore, although toxoplasma parasites may be generally harmless in a sheep's brain, clinical cases of acute cerebral toxoplasmosis do occur, some of which are perhaps not always properly diagnosed, or are probably confused with other forms of encephalitis. This may account for the scanty information about this form of toxoplasmosis in sheep.[1]

In the course of histological examination of serial sections of the brain-stem from 150 apparently healthy sheep (chosen at random from various parts of Scotland), oval or round cysts were found in 4 animals only. In 3 these cysts were 20–60 μ in diameter, and in all respects resembled sarcocysts, which are parasites commonly found in sheep striated muscle. There was no reaction in the brain tissue around the cysts, and they contained elongated or crescent-shaped basophilic bodies, tightly packed together (fig. 1). In the 4th brain, however, a different type of cyst was found; this was 30 μ in diameter, and was filled with very small eosinophilic bodies having basophilic centres and resembling toxoplasma pseudocysts (fig. 2). In my opinion the sarcocyst-like cysts were most probably misplaced parasites, while the toxoplasma-like pseudocysts in the one animal were possibly latent toxoplasma parasites.

One case of acute cerebral toxoplasmosis was observed in a 2-year-old ewe belonging to our institute, which suddenly developed a high temperature and nervous symptoms—motor irritation, excitement, trembling, continuous drawing of the head to one side, and rolling of the eyes. The animal became comatose within 24 hours of the onset of the illness, and had to be destroyed.

Macroscopic examination of the central nervous system revealed diffuse congestion of meninges and brain substance alike. Histological changes were especially severe in the brain-stem, where there were numerous severe perivascular infiltrations of several layers of plasma cells, epithelioid cells, and lymphocytes. The endothelium of the capillaries was swollen, and cells were bulging into the capillary lumen. In the cytoplasm of some of these endothelial cells small eosinophilic bodies, with dark centres resembling free toxoplasms, were present. Small miliary granulomas, composed of a mixture of large endothelial and epithelioid cells with only a few lymphocytes, were frequent (fig. 3). Similar but very large granulomas, with necrotic centres and often with large and dense infiltrations of polymorphonuclear leucocytes, were obvious. There was diffuse inflammation of brain tissue, with swelling of capillaries, multiple hæmorrhages, diffuse microglial proliferation, and degeneration or necrosis of neurones. The meninges all along the brain-stem were markedly infiltrated with lymphocytes, monocytes, and plasma cells, and similar infiltrations were observed around the nerve-roots of the cranial nerves.

The cerebrum and cerebellum were less affected, but occasional capillaries—especially at the periphery—were surrounded by wide cuffs of lymphocytes. In the hippocampal gyrus, however, a number of round or elliptical pseudocysts, measuring 12–50 μ in diameter, and containing a mass of closely packed minute eosinophilic structures with darkly staining central chromatin, were found. The brain substance in the immediate vicinity of the cysts did not show any reaction (fig. 4).

Moredun Research Institute,
Gilmerton, Edinburgh. I. ZLOTNIK.

1. Olafson, P., Monlux, W. S. *Cornell. Vet.* 1942, **32**, 176.

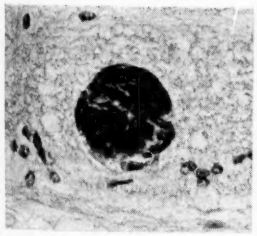


Fig. 1.

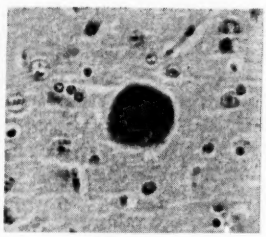


Fig. 2.

Fig. 1—Sarcocyst-like body in the brain of a normal sheep. (×420.)
Fig. 2—Toxoplasma-like pseudocyst in the brain of a normal sheep. (×420.)

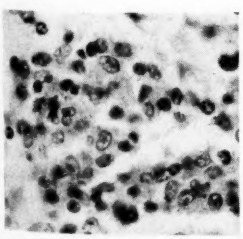


Fig. 3.

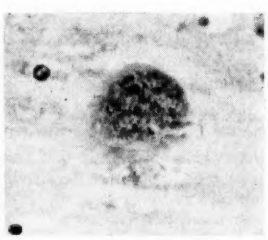


Fig. 4.

Fig. 3—Toxoplasmosis; miliary granuloma. (×850.)
Fig. 4—Toxoplasma pseudocyst. (×850.)

PATHOGENESIS OF GASTRIC ULCER

SIR,—The interesting papers of Dr. Marks and Professor Shay,[1] and of Dr. Andreassen and his colleagues [2] use arguments which may not be valid when considering the pathogenesis of gastric ulcer, especially in relation to combined gastric and duodenal ulcer.

The age distribution of combined ulcer corresponds to that of gastric ulcer alone [3–5] and differs from that of duodenal ulcer alone. If duodenal ulcer and gastric ulcer occurred independently one would anticipate owing to the difference in age distribution that, when combined ulcer was present, the duodenal ulcer would have appeared first by chance two out of three times. However, duodenal ulcer and gastric ulcer are associated more frequently than can be explained by chance, and the contribution made to combined ulcer by duodenal ulcer is likely to be double that made by gastric ulcer. One would anticipate therefore that in eight of ten cases of combined ulcer the duodenal ulcer would appear first, which does not differ significantly from Dr. Andreassen's figure. There is then no need to seek a special pathological mechanism to explain the sequence.

Taken simply, the fact that the age distribution of combined gastric and duodenal ulcer is the same as for gastric ulcer alone would not specially point to any consequence of duodenal ulcer being related to the genesis of the subsequent gastric ulcer. Not only are duodenal-ulcer subjects more likely to develop gastric ulcer than the rest of the population, but the data of Doll and Kellock [6] show that this propensity is also shared by their non-ulcer sibs.

It appears that the presence of duodenal ulcer may be of no special significance in the genesis of gastric ulcer except that gastric and duodenal ulcer patients and their sibs may be both subject to mutual influences which distinguish them from the general population. In the case of duodenal ulcer, this is what Clarke and his colleagues of Liverpool [7] appear to have found in another context.

Gastro-intestinal Clinic,
Sydney Hospital,
Sydney, N.S.W., Australia. B. P. BILLINGTON.

1. Marks, I. N., Shay, H. *Lancet*, 1959, i, 1107.
2. Aagaard, P., Andreassen, M., Kurz, L. *ibid.* p. 1111.
3. Comfort, M. W., Priestley, J. T., Dockerty, M. B., Weber, H. M., Gage, R. P., Solis, J., Epperson, D. P. *Surg. Gynec. Obster.* 1957, **105**, 435.
4. Mangold, R. *Brit. med. J.* 1958, ii, 1193.
5. Kurokawa, T., Okabayashi, A. Report to the Sixth Congress of the International Society of Geographic Pathology, 1957.
6. Doll, R., Kellock, T. D. *Ann. Eugen., Lond.* 1951, **16**, 231.
7. Clarke, C. A., Price-Evans, D. A., McConnell, R. B., Sheppard, P. M. *Brit. med. J.* 1959, i, 603.

ALCOHOL-INDUCED PAIN IN CARCINOMA

SIR,—The ingestion of alcohol may cause pain in patients suffering from Hodgkin's disease. This phenomenon has been described many times.[1–9] The first British case was recorded when a doctor suffering from Hodgkin's disease described the symptoms in himself.[10] The pain comes on usually within a few minutes of drinking and persists fifteen minutes to an hour; in addition there may be some anæsthesia after the pain has subsided.[1] The symptoms often appear several months before any tumour can be found, and may regress even though the growth is increasing in size.

James et al.[11] were the first to describe alcohol-induced pain in association with carcinoma. They reported two patients, one probably with a thymic tumour and the other with a disseminated adenocarcinoma of the pancreas. As they pointed out, neither of these cases proves conclusively that this phenomenon is associated with carcinoma, for they noted Thomson's [12] work on the association of Hodgkin's disease and thymic tumours, and also the connection between alcohol and pancreatitis.[13] In their second case autopsy showed necrosis in the tail of the pancreas and in some of the tumour; moreover both these cases had invasion of the pericardium by growth, and the pain complained of by both patients was related to the chest.

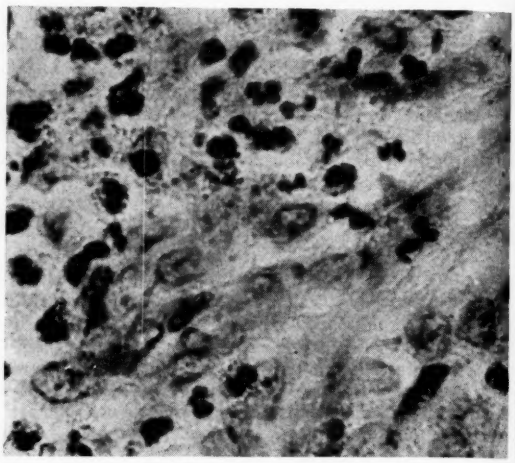
In an American review of alcohol-induced pain, Braun and Schnider [14] mentioned the case of a woman with advanced carcinoma of the breast who had pain "of extremely short duration" in a lymph-gland "invaded by an inflammatory metastatic process" a minute after taking alcohol. No other details of the case were given, but the truth of the complaint had been confirmed with control non-alcoholic drinks. In this patient the pain lasted for a very short time, which is atypical, and also the gland was described histologically as "inflammatory metastatic". Presumably this means that section showed hyperplasia and catarrh and there were some cells or clumps of cells that looked neoplastic.

I report here a case in which there were typical symptoms in a woman who had a proven carcinoma of the cervix uteri.

The patient, aged 39, was admitted to hospital on March 24, 1958, with a stage-I carcinoma of the cervix. She had had one child only, and since parturition, 28 months previously, she had had slight vaginal discharge, with 6 months' intermenstrual bleeding. While in hospital she was treated twice with intrauterine and intravaginal radium.

On the day of her discharge home, the patient spontaneously mentioned that for the previous 6 months she had had bearing-down pains whenever she took alcohol. These pains were so severe that she would have to retire from any party she was attending, and would suffer considerably for half an hour to an hour. The pains would start after a mouthful of gin or whiskey, but she might be able to finish a glass of beer before becoming affected. She had to give up drink. Her history of intermenstrual bleeding was also of about 6 months' duration but she did not seem to associate these facts. She was not of an introspective or nervous disposition, but she complained of halitosis for the past 15 years—a complaint which to some extent was justified.

As the patient was ready to leave hospital, there was not time for further investigation, but a glass of brandy (30° under proof) was pressed on her. This had no effect whatsoever, so she went away very pleased. She has had no recurrence of growth or of alcohol pain to date (December, 1958), and can drink what she wishes. She still worries about her halitosis.



Biopsy of cervix stained with hæmatoxylin and chromotrope. The cells with granular cytoplasm are eosinophils.

While in this hospital, an intravenous pyelogram was normal and showed no evidence of dilatation of the renal pelvis. A barium-meal examination had been done some time previously when her bad breath was being investigated elsewhere, and was normal.

The cervix biopsy specimen showed squamous-cell carcinoma (see figure). The only fact that seems worth noting is the infiltration with eosinophils. This is a common finding in carcinoma of the cervix, but here it may possibly have some significance.

We cannot prove that this woman had pain and have only her word for it, but she seemed completely reliable, and complained quite spontaneously. The symptoms seem clearly associated with carcinoma. An inflammation such as endometritis might conceivably be the cause (similar to the alcohol-pain which occurs in a Brodie's abscess, and in osteomyelitis[15]), but the uterine curettings were scanty, and did not appear infected. The presence of eosinophils is interesting. Gros [16] relieved alcohol-induced pain with anti-histamines. Eosinophils may act as histamine carriers [17] and eosinophil infiltration is common in Hodgkin's disease, although not an essential finding. Some sort of inflammatory reaction seems to be the basis of this phenomenon, for it has appeared in tuberculosis, sarcoid, pyogenic lymphangitis, osteomyelitis, bone fractures,[9] and pancreatitis.[12] In the case of carcinoma of the breast mentioned above there was a brief pain in an "inflammatory metastatic gland". It seems to be a property of tissue reaction rather than of neoplasm. Hodgkin's glands may recur without causing reappearance of the symptom. Godden et al.,[8] however, discount the significance of eosinophils on the grounds that the cells are not invariably present, and they favour nerve infiltration or the presence of abnormal collagen tissue.

I should like to thank Dr. Oliver Chance for permission to publish this case, and Prof. R. A. Q. O'Meara for the photomicrograph.

St. Luke's Hospital,
Dublin. J. B. HEALY.

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LOSS OF ANKLE-JERK

SIR,—We agree with much that Mr. London says (Aug. 15) in his remarks on our letter (July 11). Certainly the flattening of buttock, thigh, or calf is an important sign in many cases of sciatica, and while not noted in our subject has been noted in the large majority of cases one of us is now investigating.[1] We would agree that this sign is most likely due to a disturbance of the reflex arc(s) subserving tone, but we feel it important to stress that this arc is probably not identical with that producing the tendon jerk.[2]

Regarding the importance of an inhibitory afferent inflow causing the loss of the ankle-jerk we are less certain. If, as is usually conceded, the tendon reflexes in man are produced via monosynaptic arcs any incoming inhibitory impulses must act—if they are to depress the tendon reflex—at the appropriate anterior-horn-cell pool. Such an inhibition of anterior horn cells might be expected to produce some diminution in all activity utilising the final common path, including willed movement. We were interested to note no diminution in motor power, which suggested to us that there was no major inhibition at the level of the anterior horn cells. We concede, however, that the tendon reflexes may not be exclusively subserved by monosynaptic reflex arcs in man,[3] in which case incoming inhibitory impulses might act at internuncial level. However, the type of nerve-fibre conveying such impulses—which as Mr. London states do not reach consciousness—remains problematical.

St. Thomas's Hospital, London, S.E.1. A. J. BULLER.
St. George's Hospital, London, S.W.1. A. C. DORNHORST.

NUCLEOHISTONE AND THE L.E. FACTOR

SIR,—Your annotation of April 18 pointed out that the L.E. factor behaves in many ways as though it might be an autoantibody towards deoxyribose nucleoprotein. The following results tend to show that in systemic lupus erythematosus, rheumatoid arthritis, and polyarteritis nodosa, vascular antibodies may also be involved in the pathogenesis of the disease.

The intimal layer was removed from the aorta of a four-year-old child who had died at operation four hours previously. A homogenate in 15 ml. physiological saline was made of the intimal layers and the supernatant fluid after centrifugation was stored frozen until ready for use. This intimal extract was mixed with a polystyrene latex [4] suspension, of particle size 0·81 μ, in the following proportions: 10% intimal extract, 1% latex, 89% McIlvaine's buffer pH 5·0. Serial doubling dilutions of the sera under test from patients with systemic lupus, rheumatoid arthritis (with and without clinical evidence of arteritis), and polyarteritis nodosa were made in the range from 1:2 to 1:4096 using the pH 5·0 buffer as diluent. To each dilution was added an equal volume (0·25 ml.) of the sensitised latex particles. The tubes were incubated at 37 C for two hours, then centrifuged for three minutes at 1750 r.p.m., and the resulting agglutination read and graded 1 plus to 4 plus. Agglutination in a titre of 1 : 8 or higher was regarded as positive. Any serum causing agglutination was tested against untreated latex particles. For a positive test at least a twofold dilution difference was required between the agglutination of the sensitised and unsensitised latex particle system. Titres as high as 1:1024 were obtained; most positive titres were around 1 : 64.

The results (see table) suggest that the system may be a measure of the presence of vascular antibodies. Stefanini and Mendicoff [5] in precipitation tests with aortic intimal extract reached the same conclusion. It is unlikely that traces of gamma-globulin present in the extract (shown by zone electrophoresis) are responsible for the positive tests, since 9 out of 16 rheumatoid sera were negative when tested with intima-latex suspension, yet all had F11 hæmagglutination titres in excess of 1 : 56,000. Nor is it likely that deoxyribose nucleic acid present in the extract was responsible for the positive tests since that substance unassociated with its histone cannot be made to sensitise latex particles to produce a positive test with systemic lupus sera—only the associated nucleoprotein can be used and this, of course, is insoluble in isotonic saline which was used to extract the aorta.

RESULTS OF THE INTIMA-LATEX TESTS

Type of sera	Total no.	No. positive
Normal	4	0
Polyarteritis nodosa	5	4
Acute disseminated lupus erythematosus	7	7
Rheumatoid arthritis without arteritis	8	1
Rheumatoid arthritis with arteritis	8	4

These results, admittedly few in number, show that there is yet another tissue component apart from nucleoprotein to which the body loses tolerance in systemic lupus. They also demonstrate another antigenic system common to lupus, polyarteritis nodosa, and rheumatoid arthritis.

The work on which this letter is based was made whilst I was visiting fellow in medicine at the University of California Medical Centre and was supported by a grant from the National Institutes of Health, Arthritis and Metabolic Diseases. I am very grateful to Dr. E. Engleman and Dr. W. Epstein for their kindness and encouragement of this research.

Langley Porter Neuropsychiatric Institute, San Francisco. W. J. FESSEL.

THE MEDICAL SUPERINTENDENT

SIR,—Your authoritative and statesmanlike leader (Aug. 22) could well be the preliminary of a note from the Editor of *The Lancet* in the interesting correspondence about medical superintendents of mental hospitals which he has encouraged in his columns: " This correspondence must now cease."

But before it does, may I add one note—that, although the Mental Health Act has been widely acclaimed as following closely the recommendations of the Royal Commission, we on that Commission, according to my recollection, never talked about nor even thought about any possibility of any change in the status quo of the medical superintendent, and nothing of that appears in our report.

Guildhall, London, E.C.2. J. GREENWOOD WILSON.

MEDICAL ADMINISTRATION IN PSYCHIATRIC HOSPITALS

SIR,—In your issue of Aug. 22 Dr. Shaw and Dr. Samuel describe the administrative experiment at Belmont Hospital and say that " there is general agreement that the arrangement has worked well ". I should perhaps point out that neither the Hospital Management Committee nor the Regional Hospital Board has yet officially formulated any opinion in the matter.

St. Ebba's and Belmont Hospital Group, Sutton, Surrey. G. H. SHREEVE, Chairman, Hospital Management Committee.

GENERAL INFIRMARY AT LEEDS

Dr. S. T. ANNING (42, Park Square, Leeds, 1) writes: "I am working on the history of the General Infirmary at Leeds. I would be most grateful for information about any relevant letters, documents, portraits, &c. If any such were lent to me they would be copied and returned without delay and due acknowledgment to the owner would be made in the text."

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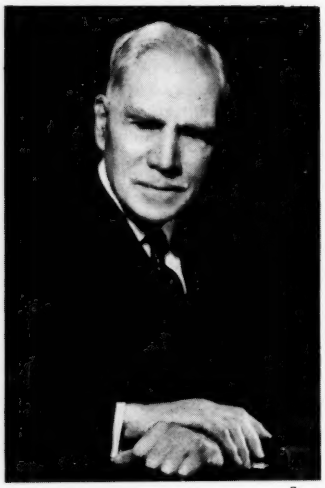
Obituary

ROBERT ARTHUR YOUNG

Kt., C.B.E., M.D., B.Sc. Lond., F.R.C.P.

Sir Robert Young was a physician who disdained neither the old nor the new. When he began to practise medicine he had still to diagnose without benefit of radiology and to treat his patients without the help of modern drugs or the support of surgical procedures. Soberly progressive, he accepted new aids which had proved their worth, but he consulted the chest X-ray only after he had completed a careful physical examination of the patient. In the earlier years of this century he was for some time *The Lancet*'s principal medical adviser; and we, like so many others, are grateful for a share of his wisdom, experience, and kindness.



Fayer

He was born in 1871, the son of William Young of a Norfolk family, and he was educated in London at the United Westminster Schools, King's College, and the Middlesex Hospital. He graduated B.SC. in 1891 and was awarded the university scholarship in physiology. Three years later he graduated in medicine with first-class honours, and in 1895 he was awarded the gold medal for his M.D. thesis. After holding house-appointments at the Middlesex Hospital and the Brompton Hospital he became medical registrar at the Middlesex and lecturer in physiology at the medical school. In 1901 he was elected to the staff of the Middlesex on the resignation of William Cayley, and about this time he also joined the staff of the Brompton. At the Middlesex his ward rounds were popular with students and patients, for his practice of medicine was based on careful examination, on logical and systematic diagnosis by elimination, and on kindness and courtesy. His sayings have become part of hospital legend. Not long ago G. E. B. recalled how in demonstrating the signs of mitral stenosis Young used to say, " You may have noticed a firm of carriage builders in Oxford Street called ' Thrupp and Maberly '. The murmur in mitral stenosis sounds like ' THRUPP ',' and he rolled the " r " and accentuated the " p " as he pronounced this onomatopœic word.

Young was elected fellow of the Royal College of Physicians in 1905, and was senior censor, Lumleian lecturer in 1929, and Harveian orator in 1939. The subject of his Lumleian lectures—surgery of the chest—was at first sight a curious choice for a physician, but his masterly review pointed the way to many of the advances of the past thirty years.

He retired from his hospital appointments in 1936. During the late war he returned again to the wards and once more delighted and surprised the students by his demonstrations of his clinical independence of X-rays. At the beginning of the National Health Service he again stepped into a breach (though this time of a different kind), and by his tactful and wise chairmanship of the new board of governors of the Hospitals for Diseases of the Chest smoothed away the difficulties of amalgamation. In 1951 he was one of the physicians who attended King George VI in his illness.

On his 80th birthday his colleagues at the Middlesex and the Brompton gave a dinner in his honour as a physician and, as more than one added, " because he is such a nice man ". K. R., who was his ward clerk, house-physician, and registrar, expands this simple affectionate tribute:

" I think what stands out in one's memory about Sir Robert was his kindness to us all, his up-to-dateness, and his adaptability. Nowhere was this adaptability better seen than in the manner in which he had orientated himself entirely to the diagnostic use of X-rays, especially in chest disease, though this was never to the exclusion of what he could find by physical examination; he could always surprise the younger man with his use of the classical method. His management of patients and of the awkward situations that sometimes arise in their affairs was an education in itself.

" Spending a bit of time in committee work was to him as uncongenial as it is to most of the rest of us. Nevertheless, he did more than his share. To single out one instance, his chairmanship of the governing body of the Hospitals for Diseases of the Chest through an awkward period will always be remembered. It was on his own insistence that he did not continue for a second term in office, because he felt it only right that, once launched, the chairmanship should fall to a younger man.

" The diversity of his interests outside medicine was striking and he was an inveterate collector. Until quite recently he might be seen in the Portobello Road on a Saturday morning, seeing what he could find to show his friends the next week. If the piece of Waterford proved later on to be something less good, he was nothing daunted but enjoyed it all. He liked dining out, whether at the College (at ' cads' corner '), the St. Albans, the Sydenham, the Savage, or a restaurant. Many of these occasions come to mind, as when once during the war, when the meat course was advertised as roast lamb, the only available wine was an Algerian burgundy, and on testing it R. A. turned to his guest and remarked ' My dear boy, we shan't want any mint sauce '.

" He was always ready and eager for new experiences of all sorts: he travelled abroad very recently, and he was an interested (and excellent) listener to the accounts of the holiday adventures of others—especially if they included some pictures of antiquities. To the end he made a point of finding common ground with young doctors, often quite newly qualified, and with young people generally. Truly a gentleman and a great physician has gone from us."

He married Fanny Caroline Phoebe Kennedy, who died in 1944. Their only son survives them with the three grandsons whose companionship was one of the greatest pleasures of Sir Robert's active retirement. At the end of July, some of his friends were glad to welcome him as usual at a College dinner. He died three weeks later on Aug. 22 in London.

A memorial service will be held at the royal parish church of St. Martin-in-the-Fields, on Monday, Sept. 7, at noon.

FRANCIS HUGH TEALE

K.C.V.O., M.D., B.Sc. Lond., F.R.C.P.

Sir Francis Teale, whose death on Aug. 22 we announced last week, was honorary officer in charge of the immunotherapy department at University College Hospital and lecturer on immunotherapy at the medical school. He was also honorary bacteriologist to the Radium Beam Research Institute.

He graduated B.SC. from University College in 1895 and M.B. two years later. He spent years of postgraduate study in Frankfort-on-Main and in Berlin. He proceeded to the degree of M.D. in 1898.

In 1913 he was elected F.R.C.P. and in 1918 he delivered the Dobell lecture at the college. He chose as his subject bacterial intoxication, and he described observations which

he had made with E. Bach, on the bacteria themselves and on infected animals, which suggested that the intoxication caused by infection might be compared to the poisoning produced from damaged muscles during wound shock. The following year he gave the Ringer lecture at University College. He was appointed C.V.O. in 1944 and promoted K.C.V.O. in 1951—honours which are awarded for services to the Royal Family. He was also a chevalier of the Royal Order of St. Olaf.

He married Dorothea Felsen, who survives him.

ERIC JAMES NEILL

B.A., M.B. Cantab.

Dr. E. J. Neill died at the age of 55 on Aug. 11 at Newhaven, where he had practised for many years.

He was one of four sons of two doctors; but his father, having qualified, left medicine and was ordained. He was educated at Dean Close School and, when his father moved, at St. Paul's School, where he won a classical scholarship to Caius. He took his honours classics degree, but realised that schoolmastering was not his life and went to Barts, his father's hospital, where he qualified in 1929. After a short time in Ipswich, he settled in Newhaven. During the late war he served at sea with the Fleet Air Arm. He was never so fully fit afterwards, but continued to work arduously, for, with his busy practice, he was also Admiralty surgeon and agent and Treasury medical officer, and it was his duty to meet cross-Channel boats.

W. A. B. writes:

"Eric grew up in the atmosphere of parish work among working people. He stayed happiest in this throughout his life, so that when his old chief, Wilfred Shaw, told him later how much better he could have done in a London practice he said, 'You know, I grew up in a parish and these working people are what I want.' He used his great knowledge of local conditions and people forcefully on the urban district council. Indeed, he disliked leaving Newhaven, and so confined his recreations to tennis and captaincy of the town hockey side. He loved caravanning holidays and, most of all, his home. Here, with his wife—who shared his life very fully—he was always waiting to help his people, and his father's ideals were strong in him. Very few have such warm or determined hearts."

Dr. Neill leaves a widow and a son.

CORNELIUS PACKARD RHOADS

M.D. Harvard, D.Sc., LL.D.

Dr. C. P. Rhoads, director since 1945 of the Sloan-Kettering Institute, New York City, and since 1953 scientific director of the Memorial Center for Cancer and Allied Diseases, died on August 13 at his summer home at Stonington, Connecticut.

He was born at Springfield, Mass., in 1898, and graduated A.B. at Bowdoin College in 1920, and M.D. (*cum laude*) from Harvard Medical School in 1924. After serving a year's internship in surgery at the Peter Bent Brigham Hospital in Boston under Harvey Cushing, he successively became Trudeau fellow at the Trudeau Sanatorium in New York State, instructor in pathology at Harvard, assistant pathologist to the Boston City Hospital, and associate, then associate member, of the Rockefeller Institute for Medical Research in New York. In 1940 he was appointed director of the Memorial Hospital, and professor of pathology at Cornell University Medical College. Between 1943 and 1945 he served as colonel in the Medical Corps of the United States Army, and as chief of the Medical Division of the Chemical Warfare Service, in which capacity he directed the toxicological research laboratory at Edgewood Arsenal, Md., and the medical laboratory at Dugway Proving Ground in Utah, and set up testing stations in Florida and the Panama Canal Zone. During this period he was also chairman of the blood-procurement programme, and vice-chairman of the National Research Council's committee on the treatment of gas casualties. After the war, he was appointed special consultant on cancer to the United States Public Health Service and consultant at the Brookhaven National Laboratories of the Atomic Energy Commission.

His greatest opportunity came in 1945, on appointment to the directorship of the Sloan-Kettering Institute, when with his unique vigour and a kind of impatient boldness he took a leading part in the post-war expansion of cancer research. In that decade he not only carried heavy administrative and organisational responsibilities but also performed yeoman service in many other capacities.

He was chairman of the Committee on Growth, member of the advisory committee of the Chemical-Biological Coordination Center, member-at-large of the Division of Medical Sciences of the National Research Council, member of the board of directors and executive committee of the American Cancer Society, member of the cancer chemotherapy committee of the Public Health Service, trustee of the Charles F. Kettering Foundation, vice-president of the American Association for the Advancement of Science and chairman of its section on medical sciences, and member of the American Association for Cancer Research—to name but a few. In formal recognition of his work Dr. Rhoads had been made honorary D.Sc. of Bowdoin College and of Williams College, and LL.D. of the University of Saskatchewan. He was a member of the U.S. Legion of Merit and received the Cleveland medal award, the American Cancer Society award, and the Walker prize of our own Royal College of Surgeons of England.

A. H. writes:

"In these last years Rhoads became an outstanding American public figure and indeed character. Perhaps over-purposeful, and over-reliant on what he called the frontal attack—in part because of its resounding success in the fields of industry and atomic energy—nevertheless he possessed a comprehension of the philosophy of research which is not sufficiently known. In particular he found little support for the theme that idleness breeds inspiration, and his viewpoint is perhaps best expressed in an address which he delivered to the Edison Foundation last May on Men and Motivation. During his working life—all too short to show the results which must gradually flow—he was author or coauthor of upwards of two hundred papers on subjects as diverse as the tuberculin reaction, argyria, endocarditis, poliomyelitis, renal metabolism, sprue, hookworm infection, pernicious anæmia, porphyria, the clinical pathology of cancer of the gastrointestinal tract, steroid excretion, carcinogenesis, and chemotherapy. Yet his greatest contribution may be found to lie in the opportunities he made available to others, and in the realisation—to quote his own words—that 'the function of the good laboratory operating with a definite goal is to give the greatest stimulus, opportunity and freedom to the basic investigator in fields pertinent to the ends desired'.

"No man could question his courage or dedication. But we also recall the humour and kindliness with which they were blended, will remember 'Dusty' in the name by which he was universally and affectionately known, and will wish to share both pride and loss, both with his staff and with his wife who did so much to support and sustain him."

Appointments

BARKER, ROSETTA C., M.B. Belf., D.P.H.: M.O.H., Shoreham-by-Sea, Southwick, and Chanctonbury.

KEANE, KATHLEEN, M.B. N.U.I., D.OBST., D.P.H.: senior assistant M.O., maternal and child health services, Worcestershire.

Manchester Regional Hospital Board:

DAVID, J. P. D., M.D. Wales, assistant physician (S.H.M.O.) in geriatrics, Bolton and district hospitals.

DENMARK, J. C., M.B. Lpool, D.P.M.: assistant psychiatrist (S.H.M.O.), Bolton and district group of hospitals.

DOUGLAS, W. K., M.B. Cantab., F.R.C.S.: part-time consultant thoracic surgeon, South Manchester and West Manchester groups of hospitals.

LIU, MEI-CHEN, M.D. Cheeloo, L.M.S.S.A., D.P.M.: assistant psychiatrist (S.H.M.O.), Brockhall Hospital, Langho, near Blackburn.

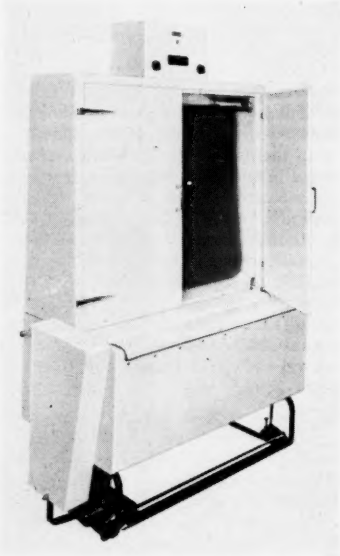
TWEEDY, P. S., M.D. Lond., M.R.C.P.: part-time consultant geriatrician, Stockport and Buxton group of hospitals.

Notes and News

A MACKINTOSH SHEET WASHER AND DRIER

Dr. J. V. MORRIS, medical superintendent of Little Plumstead Hospital, near Norwich, writes about a unit designed to replace by a simple mechanical process the traditional method of washing and drying mackintosh sheets.

The washer comprises a tank containing two contrarotating brushes, which is filled with disinfectant solution by a constant feed and emptied to a soil drain. The brushes are driven by an electric motor, and they may be separated by a foot pedal. The drier is a cabinet with double doors, fitted with pullout racks to take 4 sheets, and supplied with hot air from a blower, which is controlled by two switches mounted above (see figure). The overall dimensions are height 5 ft. 6 in., width 4 ft. 2 in., and depth 2 ft.



To operate, the machine is switched on, the foot pedal depressed, the sheet fed into the slot on top of the tank, and the pedal released. The sheet is thus drawn gently into the tank against the pressure of the operator's hands, and is withdrawn at the end. The wet sheet is adjusted on a roller of the drying cabinet, and the process is repeated until the cabinet is full. The sheets dry in 10–12 minutes.

The design of the machine was conceived by the nursing and medical staff of Little Plumstead Hospital, and the engineering details were adapted to the hospital's requirements by Tullis Industries Ltd., Mill Corner, Gerrards Cross, Bucks, who have applied for a patent and will market the machine as the " Little Plumstead Mackintosh Sheet Sluicer and Drier ".

SYMPOSIUM ON CARDIOVASCULAR DISEASE

THE first International Symposium on Cardiovascular Disease to be arranged in South America was held in Bogota, Colombia, at the Foundation A. Shaio on July 27–31. It was attended by many leading cardiologists and cardiac surgeons, particularly from the U.S.A. Among the more important topics was a discussion of the place of electrocardiography in the diagnosis of heart-disease; Dr. D. Sodii-Polaris, of the Institute of Cardiology, Mexico City, demonstrated the mastery of this investigation by his group. Another interesting session was devoted to pulmonary hypertension; research in South American cities situated at high altitudes is likely to yield further knowledge of this disorder. Discussions of the treatment of heart-disease were inevitably dominated by cardiac surgeons who had successfully exploited the advantages of the open technique using heart-lung machines. Dr. C. W. Lillehei, of Minnesota, insisted on the practicability of repairing valvular lesions of all types as well as the more usual congenital defects. He demonstrated techniques developed to this end, including the insertion of an artificial prosthesis for both the mitral and the aortic valves.

The Shaio Foundation was established in 1957 by an association of doctors in Bogota and a bequest from the late Mr. Abood Shaio. It is specifically for the diagnosis and treatment of cardiovascular disease and now has excellent facilities. The meeting, arranged by the Foundation, was rewarding and successful.

University of London

The degree of M.D. has been awarded to the following:

John Eastwood, Peter Jordan, D. B. Shaw.

Medical Research Council Fellowships

Applications are invited for the following travelling fellowships and scholarships available through the Medical Research Council for 1960–61:

(1) Rockefeller travelling fellowships, (2) United States Public Health Service fellowships, (3) Lilly foreign fellowships, (4) Lederle travelling fellowship, (5) Dorothy Temple Cross research fellowships in tuberculosis, (6) Alexander Pigott Wernher travelling fellowships in ophthalmology and otology, (7) French exchange scholarships in medical science. Application forms may be had from the secretary of the Council, 38, Old Queen Street, Westminster, S.W.1, and the closing date for applications is Oct. 31.

International Health Identity Card

According to the Swedish International Press Bureau, Dr. Ored Arner and Dr. Matt Halldin, in the *Svenska Läkartidningen*, propose that people travelling in foreign countries should carry an international identity and medical card bearing the information needed if they have an accident or acute illness. Such a card would give personal details, as well as recording the owner's blood-group, past immunisation, hormone treatment, and particular allergies, and whether he has epilepsy or diabetes. It is further suggested that the card might be combined with a driving licence, and that it should be printed in several languages.

British Institute of Radiology

A radiobiology meeting will be held at the Institute, 32, Welbeck Street, London, W.1, on Friday, Sept. 18, at 2.15 P.M. Prof. J. Rotblat will be in the chair, and Dr. W. M. Court Brown will describe a recent visit to the Atom Bomb Casualty Commission at Hiroshima. Other speakers will include Dr. Benjamin Jolles and Dr. R. H. Mole.

Dental Technicians

The National Joint Council for the Craft of Dental Technicians are introducing a scheme of voluntary registration. The register will come into operation on Jan. 1, 1960, and the principal condition for admission will be five years' apprenticeship or not less than five years' practical experience. Forms of application may now be obtained from the registrar, Dental Technicians Registration Committee, 188, Wilmslow Road, Manchester, 14.

B.M.A. Clinical Meeting

The British Medical Association will hold their second annual clinical meeting at Norwich from Oct. 22 to 25. The programme will include symposia on anticoagulants and on hospital infections.

Royal Medical Benevolent Fund

The annual general meeting of this fund will be held on Wednesday, Sept. 30, at 5 P.M., at 11, Chandos Street, London, W.1.

The Institute of Neurology, London

On Thursday, Sept. 10, at 5.30 p.m., at the National Hospital, Queen Square, W.C.1, Sir John Eccles, of the Australian National University, will give a lecture on Plasticity Changes in the Nervous System.

Mr. H. R. Thompson has been elected master of the Barber-Surgeons' Company for the coming year.

Surgeon Captain G. L. Foss, R.N.R., has been appointed an honorary physician to the Queen, in succession to Surgeon Captain R. S. Rudland.

CORRIGENDUM: *Gastrointestinal Protein Loss in Severe Malabsorption Complicated by Idiopathic (Hypercatabolic) Hypoproteinæmia.*—The title of this article (Aug. 8, p. 85) was printed wrongly as *Hyperproteinæmia.*